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DOI: 10.1016/j.cortex.2016.02.005

Document Version Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):

Cassel, A., Morris, R., Koutroumanidis, M., & Kopelman, M. D. (2016). Forgetting in temporal lobe epilepsy: when does it become accelerated? *Cortex*, *78*, 70–84. https://doi.org/10.1016/j.cortex.2016.02.005

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# Accepted Manuscript

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PII: S0010-9452(16)30007-7

DOI: 10.1016/j.cortex.2016.02.005

Reference: CORTEX 1683

To appear in: Cortex

Received Date: 31 August 2015

Revised Date: 5 January 2016

Accepted Date: 8 February 2016

Please cite this article as: Cassel A, Morris R, Koutroumanidis M, Kopelman M, Forgetting in temporal lobe epilepsy: when does it become accelerated?, *CORTEX* (2016), doi: 10.1016/j.cortex.2016.02.005.

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# Forgetting in temporal lobe epilepsy: when does it become accelerated?

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#### Abstract

The notion of 'accelerated long-term forgetting' has often been attributed to disrupted 'late' memory consolidation. Nevertheless, methodological issues in the literature have left this theory unproven, leading some to suggest such findings may be reflective of subtle acquisition or early retention deficits. This study attempts to address such issues, and also to explore which pathophysiological variables are associated with forgetting rates. Eighteen participants with temporal lobe epilepsy (TLE) and eighteen matched controls completed background neuropsychological measurement of immediate and short-delay memory that showed comparable performance, both on verbal and visual tests. Using two novel experimental tasks to measure long-term forgetting, cued recall of verbal and visuospatial material was tested 30 seconds, 10 minutes, one day, and one week after learning. Forgetting of verbal material was found to be progressively faster during the course of a week in the TLE group. For visuospatial memory, participants in the TLE group exhibited faster early forgetting in the first 10 minutes after learning, as indicated by planned comparisons, with comparable forgetting rates thereafter. Our findings provide evidence for two patterns of disruption to 'early' memory consolidation in this population, occurring either at the initial delay only or continuing progressively through time. Differences in how soon after learning accelerated forgetting was detectable were related to factors associated with greater severity of epilepsy, such as presence of medial temporal lobe sclerosis on MRI and use of multiple anti-epileptic agents.

Keywords: temporal lobe epilepsy; forgetting; accelerated long-term forgetting; memory consolidation; anterograde memory measures

#### 1. Introduction

Interest in forgetting rates in temporal lobe epilepsy (TLE) has helped inform our knowledge of memory consolidation processes. Such patients are often studied in this regard as medial temporal lobe disruption and associated damage provides a useful paradigm for investigating the mnemonic function of this brain region. Consolidation can be defined as the stabilisation of long-term declarative memories post-acquisition, thought to occur as a dual process, involving synaptic ('early') and systems ('late') consolidation (Dudai, 2004). Within this theoretical framework, synaptic modification of memory neural networks occurs in the first minutes to hours after learning within the hippocampal network, whilst systems consolidation involves the reorganisation of medial temporal and neocortical structures over much longer timescales (Dudai, 2004). The extent to which declarative memory engrams eventually become hippocampal-independent, or continue to rely on this region each time traces are activated, is a controversial issue, with a number of competing theories in existence (Alvarez & Squire, 1994; Nadal & Moscovitch, 1997; Winocur & Moscovitch, 2011).

Some have described a pattern of memory decay known as 'accelerated long-term forgetting', thought to be related to deficits in memory consolidation (Butler, Mulhert, & Zeman, 2010; Butler & Zeman, 2008b; Fitzgerald, Mohamed, Ricci, Thayer, & Miller, 2013; Hoefeijzers, Dewar, Della Sala, Zeman, & Butler, 2013). This notion refers to findings that people with TLE can appear to perform 'normally' on standard neuropsychological anterograde memory tests (where recall is typically assessed within 30 to 45-minutes following new learning) yet show evidence of faster forgetting at later, 'long-term', delay intervals. It has been argued that this phenomenon is indicative of disrupted 'late' memory consolidation but, at present, this theory remains unproven (Hoefeijzers et al., 2013). Exploring what pathophysiological variables are implicated in this type of forgetting could further provide insight into this phenomenon: clinical and subclinical seizure activity (Jokeit,

Daamen, Zang, Janszky, & Ebner, 2001; Mameniskiene, Jatuzis, Kaubrys, & Budrys, 2006; Wilkinson et al., 2012); sclerosis in the medial temporal lobe (Mulhert et al., 2011; Wilkinson et al., 2012); and use of anti-epileptic medication (Jokeit, Krämer, & Ebner, 2005) have all been shown to be associated with accelerated forgetting rates in epilepsy patients. However, the extent to which these variables contribute to forgetting is not clear; findings are heterogeneous because of the wide variability of clinical features and cognitive profiles in this population (Butler et al., 2010; Fitzgerald, Mohamed, et al., 2013; Kwan & Brodie, 2001).

Despite this growing literature base, research on forgetting in healthy participants and non-epilepsy patient groups has long highlighted important aspects of method or technique, which need to be addressed before inferences can be drawn about forgetting rates. These include: (1) the need to 'match' the starting point from which forgetting is measured; (2) the advantages/disadvantages of different techniques for this matching; (3) avoiding ceiling and floor effects; (4) consideration about whether forgetting should start being measured during or immediately following stimulus presentation; (5) the nature of the distraction activity between test intervals; and (6) whether repeated or equivalent material should be tested at different delay intervals (Brooks & Baddeley, 1976; Green & Kopelman, 2002; Huppert & Piercy, 1977, 1978; Isaac & Mayes, 1999a, 1999b; Kopelman, 1985, 1997, 2000b; Kopelman & Stanhope, 1997; Mayes, 1988; Mayes & Downes, 1997; McKee & Squire, 1992; Slamecka & McElree, 1983). Reviewing the epilepsy literature, Elliott, Isaac, and Mulhert (2014) published a methodological critique of forgetting studies, which additionally included comments on the need to use both verbal and visual forgetting measures, and the importance of appropriate matching of groups on demographic and cognitive variables. Elliott et al. (2014) noted that very few of these epilepsy studies have been methodologically robust. This

seriously limits the validity of the epilepsy findings, and conclusions made within the current literature with regards to when, during stabilisation, declarative memory traces are disrupted.

Another factor important in the design of forgetting studies, and subsequent conclusions made, concerns the delays over which long-term memory is assessed. Table 1 summarises studies in TLE (including participants with transient epileptic amnesia). It includes information regarding the delay periods measured, whether significant accelerated forgetting was observed, and observations on the forgetting rate curves obtained in these studies. This Table indicates that there is great variability in the literature regarding *when* memory is assessed and the *number* of delay intervals used. Further, it is evident in the majority of studies that the precise period over which accelerated forgetting manifested was often reflective of the time points measured: most found faster forgetting by the first or second delay interval measured after learning of new material (see Table 1, Delay Trials column). Moreover, some studies did not report learning performance (Dewar, Hoefeijzers, Zeman, Butler, & Della Sala, 2015; Gallassi et al., 2011; Hoefeijzers, Dewar, Dalla Sala, Butler, & Zeman, 2014; Jansari, Davis, McGibbon, Firminger, & Kapur, 2010; Lah, Mohamed, Thayer, Miller, & Diamond, 2014; McGibbon & Jansari, 2013; Narayanan et al., 2012; O'Connor, Sieggreen, Ahern, Schomer, & Mesulam, 1997; Ricci, Mohamed, Savage, Boserio, & Miller, 2015; Tramoni et al., 2011). In others, learning performance was not equated (Bell, 2006; Bell, Fine, Dow, Seidenberg, & Hermann, 2005; Cronel-Ohayon et al., 2006; Giovagnoli, Casazza, & Avanzini, 1995; Holdstock, Mayes, Isaac, Gong, & Roberts, 2002; Lucchelli & Spinnler, 1998; Mameniskiene et al., 2006; Mayes et al., 2003). These omissions or oversights limit the implications of these studies, as the role of subtle acquisition deficits cannot be excluded.

Of the studies in Table 1 that measured recall at multiple delay intervals, visual inspection of forgetting curves can provide some insight into the point at which memory

consolidation is disrupted. For instance, a progressive pattern of forgetting, in which patients start forgetting faster than controls immediately after learning, which becomes more pronounced with time, would suggest an impairment in consolidation from the 'early' stages onwards (even if between-group interactions do not become significant until later timepoints). On the other hand, forgetting curves that are parallel (or identical) for a period of time, but *then* diverge would be indicative of a disruption to 'late' memory consolidation. Reviewing the studies listed in Table 1, approximately half exhibited progressive forgetting soon after learning that eventually became statistically significant at longer delays (Atherton, Nobre, Zeman, & Butler, 2014; Bengner et al., 2006; Butler et al., 2007; Deak, Stickgold, Pietras, Nelson, & Bubrick, 2011; Evans, Elliott, Reynders, & Isaac, 2014; Kemp, Illman, Moulin, & Baddeley, 2012; Mameniskiene et al., 2006; Martin et al., 1991; Mulhert et al., 2011; Mulhert, Milton, Butler, Kapur, & Zeman, 2010; Wilkinson et al., 2012). Other studies showed a divergent pattern of forgetting, although some of these also exhibited ceiling effects (Blake, Wroe, Breen, & McCarthy, 2000; Butler et al., 2007; Butler, Kapur, Zeman, Weller, & Connelly, 2012; Butler & Zeman, 2008a; Evans et al., 2014; Hoefeijzers et al., 2013; Kapur et al., 1997; Manes, Graham, Zeman, de Luján Calcagno, & Hodges, 2005; Mayes et al., 2003; Mulhert et al., 2011; Wilkinson et al., 2012). The influence of ceiling effects is particularly important in these cases because of the potential for overlearning, which may mask any (early) differential forgetting effects between groups.

In light of such findings, some have argued that accelerated long-term forgetting may reflect a subtle acquisition deficit, or an early consolidation deficit, which subsequently affects long-term memory retention (Bell et al., 2005; Kopelman, 2000a, 2002). In this study, therefore, we aimed to investigate (after appropriate matching of initial learning) whether and when faster forgetting would be observed in a sample of TLE patients, compared with healthy controls. We hypothesised that:

(1) TLE participants would forget newly learned (verbal and visual) material faster than control participants;

(2) on examining epilepsy-related variables, more severe TLE cases would show faster forgetting than milder TLE cases (as indicated by such factors as experience of manifest seizures, polypharmacy, and medial temporal sclerosis on MRI); and

(3) any differences in forgetting rate would arise soon after learning, reflecting a deficit in 'early' consolidation in TLE patients, rather than arising de novo after a period of 'normal' forgetting (which would reflect a deficit in 'late' consolidation).

Authors (year)	Type of Study	Sample	Delay Trials	Faster Forgetting At:	Acceler	ated Forg	etting Curve			
					Progress	sive <sup>1</sup>	Divergent <sup>2</sup>	Learning Not Reported or Not Equated	Ceiling Effects	Comments
					Con	tinues	At	-		
Bell (2006)	GS	TLE	Imm 30m 2w	Not found	U	nul:	Interval:	$\checkmark$		
Bell et al. (2005)	GS	TLE	Imm 30m 24h	Not found				$\checkmark$		
Dewar et al. $(2005)$	GS	TEA	5m, 2, 5h, 7, 5h, 24h	Not found				$\checkmark$		
Dewar et al. (2013)	05	12/1	1w	riot found						
Giovagnoli et al. (1995)	GS	TLE	1h, 24h, 3d, 6d, 13d	Not found		$\checkmark$		$\checkmark$		
Kemp et al. $(2012)^3$	SCS	TEA	Imm, 20m, 4d, 11d,	Not found						Patient EB
r · · · · · · · · · · · · · · · · · · ·			30d		$\sim$					
Kemp et al. $(2012)^3$	SCS	TLE	Imm, <b>20m</b> , 4d, 11d,	20 minutes	✓ 1	1d				Patient SK
			30d							
McGibbon and Jansari (2013)	SCS	TEA	5m, 30m, <b>55m</b> , 4h,	55 minutes				$\checkmark$		
			24h							
Wilkinson et al. $(2012)^3$	GS	TLE	Imm, <b>1h</b> , 6w	1 hour	$\checkmark$ (	ów				LHS group (verbal
										task) only
Hoefeijzers et al. (2014)	GS	TEA	30m, 3h, 8h, 24h, 1w	8 hours				$\checkmark$		
Atherton et al. (2014)	GS	TEA	Imm, 30m, 12h	12 hours	$\checkmark$					Wake condition only
Deak et al. (2011)	GS	TLE	Imm, 30m, 12h	12 hours	$\checkmark$				$\checkmark$	
Bengner et al. (2006)	GS	TLE &	Imm, <b>24h</b>	24 hours	$\checkmark$					
-		IGE								
Jansari et al. (2010)	SCS	TEA	30m, <b>24h</b> , 1w, 2w,	24 hours				$\checkmark$	$\checkmark$	Ceiling effects on
			4w							recognition tasks
Lah et al. $(2014)^3$	GS	TLE	30m, <b>24h</b> , 1w	24 hours				$\checkmark$		HS and PL groups
Martin et al. (1991)	GS	TLE	Imm, 30m, <b>24h</b>	24 hours	$\checkmark$					
Mulhert et al. (2010)	GS	TEA	WL: Imm, 40s, <b>24h</b> ,	24 hours	✓ 3	Sw				
			1w, 3w							
			SC: ≈3h, <b>24h</b> , 1w, 3w	24 hours				$\checkmark$		
O'Connor et al. (1997)	SCS	TLE	2h, <b>24h</b> , 48h, 72h, 1w	24 hours				$\checkmark$	$\checkmark$	
Ricci et al. (2015)	GS	TLE	30m, <b>24h</b> , 4d	24 hours				$\checkmark$		
Butler et al. (2007)	GS	TEA	Imm, 30m, <b>1w</b> , 3w	1 week	$\checkmark$		✓ 30m		$\checkmark$	Progressive: verbal
										Divergent: visual
										Ceiling effects: both
							ć		,	tasks
Butler and Zeman (2008a)	SCS	TEA	Imm, 30m, <b>1w</b> , 3w	1 week			✓ 30m		<b>√</b>	
Butler et al. (2012)	GS	TEA	Imm, 30m, <b>1w</b>	1 week			✓ 30m	,	$\checkmark$	
Cronel-Ohayon et al. (2006)	SCS	TLE	Imm, 60m, <b>1w</b> , 29d	1 week				$\checkmark$		

Table 1. Overview of the intervals at which faster forgetting has been measured and observed in the epilepsy literature

Evans et al. (2014)	GS	TLE	24 or 45s, 30m, <b>1w</b>	1 week	$\checkmark$	✓	30m			Progressive: verbal tasks Divergent: spatial recall
Gallassi et al. (2011)	SCS	TLE	30m, <b>1w</b>	1 week				$\checkmark$		
Hoefeijzers et al. (2013)	GS	TEA	Imm, 30m, <b>1w</b> , 3w	1 week		$\checkmark$	30m			
Lah et al. $(2014)^{3}$	GS	TLE	30m, 24h, <b>1w</b>	1 week				$\checkmark$		NH and GL groups
Lucchelli and Spinnler (1998)	SCS	TLE	Imm, 10m, 60m, 24h, <b>1w</b> , 41d	1 week				~	$\checkmark$	Learning not equated: verbal task Ceiling effects: visual
Holdstock et al. (2002)	SCS	TLE	20s, 24h, <b>3w</b>	3 weeks		$\left( \right)$		✓	$\checkmark$	task
Mayes et al. (2003)	SCS	TLE	20s, 30m, <b>3w</b>	3 weeks	S	· ·	30m	✓	~	Learning not equated: verbal and visual recall and recognition tasks Divergent: word recognition N.B. also ceiling effect
Mulhert et al. (2011)	GS	TLE & IGE	40s, 30m, <b>3w</b>	3 weeks	A P	~	30m			Progressive: story recognition Divergent: visual item recall, descriptive recall
Mameniskiene et al. (2006)	GS	TLE	Imm, 30m, 4w	4 weeks	$\mathbf{Y}_{\mathbf{V}}$			$\checkmark$		Visual task only
Narayanan et al. (2012)	GS	TLE	30m, <b>4</b> w	4 weeks				$\checkmark$		2
Kapur et al. (1997)	SCS	TLE	Imm, 30m, <b>6w</b>	6 weeks		$\checkmark$	30m			
Manes et al. (2005)	GS	TEA	Imm, 30m, <b>6w</b>	6 weeks		$\checkmark$	30m			Verbal task only
Tramoni et al. (2011)	GS	TLE &	1h, <b>6w</b>	6 weeks				$\checkmark$	$\checkmark$	Ceiling effects on
Wilkinson et al. $(2012)^3$	GS	TEA TLE	Imm. 1h. <b>6</b> w	6 weeks		~	1h			recognition tasks RHS group (verbal
										task) only
Blake et al. (2000)	GS	TLE	Imm, 30m, 8w	8 weeks		$\checkmark$	30m		$\checkmark$	· ·

<sup>1</sup>Progressive: Patient group started to forget faster than control participants from last learning trial onwards

<sup>2</sup>Divergent: Patient group did not start to forget faster than control participants until a specified time point after learning

<sup>3</sup>Significant forgetting detected across different timeframes, therefore listed twice in Table

Index: GL = good learners, GS = group study, h = hour(s), HS = hippocampal sclerosis, IGE = idiopathic generalised epilepsy, Imm = immediate delay, LHS = left hippocampal sclerosis, m = minutes, NH = normal hippocampus, PL = poor learners, RHS = right hippocampal sclerosis, SCS = single case study, TEA = transient epileptic amnesia, TLE = temporal lobe epilepsy, w = week(s)

#### 2. Materials and Methods

#### 2.1 Participants

Eighteen patients with TLE were recruited from three sites across St Thomas' Hospital and King's College Hospital in London, UK. In each case the diagnosis of TLE was made based on appropriate history including seizure manifestations (Gil-Nagal & Risinger, 1997) and epileptiform activity over the temporal areas (Koutroumanidis et al., 2004). Patients were recruited if they met the following eligibility criteria: (a) between 18 and 65 years of age, (b) fluent in written and spoken English, (c) no history of neurosurgery, and (d) no neurological, medical, psychiatric, substance misuse or developmental co-morbidities. The clinical characteristics of each patient are shown in Table 2.

Eighteen age-, gender-, education-, and intelligence-matched neurologically healthy control participants who met the above eligibility criteria were also recruited via an email advertisement within King's College London and poster advertisement in the community.

The study was approved by the National Health Service National Research Ethics Service, London – Central and East Research Ethics Committee (13/LO/0399). All participants gave their written, informed consent in accordance with the Declaration of Helsinki.

ID	Age	Gender	Age of Onset	Duration (years)	Seizure Types	Medication	Laterality (EEG)	MRI	Seizure Activity During Week
1	40	М	36	4	SPS; GTC	CBZ	Bilateral	Not available <sup>1</sup>	Ň
2	35	F	15	20	CPS	CBZ; LCM	R	Normal	Ν
3	50	F	31	19	CPS; GTC	LCM	Bilateral	L MTS	Ν
4	48	М	39	9	CPS	LTG	Not available <sup>1</sup>	Not available <sup>1</sup>	Ν
5	21	М	1	20	CPS; GTC	CBZ; LTG; BMZ	R	Normal	Y: CPS, GTC
6	51	F	13	38	SPS; CPS; GTC	SVP	L	Normal	Ν
7	19	F	11	8	CPS	LEV; CBZ	L	Normal	Ν
8	36	М	16	20	CPS; GTC	LTG; LEV	L	CG L HC Abnormal	Y: CPS
9	53	М	24	29	CPS	LEV; CBZ	Bilateral	Bilateral MTS	Ν
10	48	F	27	21	SPS; CPS; GTC	None	R	Normal	Y: SPS
11	38	F	22	16	SPS; GTC	LEV	Not available <sup>1</sup>	Normal	Ν
12	39	М	32	7	CPS; GTC	CBZ	L	Normal	Ν
13	38	F	4	34	SPS; CPS; GTC	LEV; LCM	R	R MTS	Y: CPS
14	25	М	22	3	SPS; GTC	CBZ-CR	L	Normal	Ν
15	45	F	21	24	SPS; GTC	CLB; LTG; LCM	R	Normal	Ν
16	40	F	18	22	SPS; GTC	LTG	L	Normal	Y: SPS
17	38	М	14	24	SPS; CPS; GTC	OXC	R	Normal	Ν
18	44	М	20	24	CPS	LTG; CBZ	Bilateral	Normal	Ν

Table 2. Clinical characteristics of participants with TLE

<sup>1</sup>Not available in cases where diagnosis made outside of King's Health Partners hospitals

Index: BMZ = Buccal midazolam, CBZ = Carbamazepine, CBZ-CR = Carbamazepine retard, CG = Congenital, CLB = Clobazam, CPS = complex partial seizures, EEG = electroencephalography; F = female, GTC = generalised tonic clonic, HC = Hippocampus, L = Left, LCM = Lacosamide, LEV = Levetiracetam, LTG = Lamotrigine, M = male, MRI = magnetic resonance imaging, MTS = medial temporal sclerosis, N = no, OXC = Oxcarbazepine, R = Right, SPS = simple partial seizures, SVP = Sodium valproate, Y = yes

#### 2.2 Procedure

Each participant attended a two hour testing session that incorporated a neuropsychological test battery, completion of the first two recall trials of the anterograde forgetting tasks, and the presentation of the remaining task material. Participants with TLE were asked about recent seizure activity during the testing session and during their follow-up telephone calls.

#### 2.3 Neuropsychological Tests

Standard neuropsychological tests were used to assess estimated pre-morbid intellectual functioning (National Adult Reading Test – Revised Version [NART-R]; Nelson & Willison, 1991) and general intelligence (Wechsler Abbreviated Scale of Intelligence – II [WASI-II]; Wechsler, 2011). Immediate and delayed, verbal and visual memory were evaluated on the Word Lists and Visual Reproduction subtests of the Wechsler Memory Scale – Third Edition (WMS-III; Wechsler, 1997). Naming was tested using the Graded Naming Test (GNT; McKenna & Warrington, 1983) and executive function on the Hayling and Brixton tests (Burgess & Shallice, 1997). Depression and anxiety were measured using the Beck Depression Inventory – Second Edition (BDI-II; Beck, Steer, & Brown, 1996) and Beck Anxiety Inventory (BAI; Beck & Steer, 1993) respectively. Self-ratings of everyday memory problems and spatial navigation ability were assessed on the Everyday Memory Questionnaire – Revised Version (EMQ-R; Royle & Lincoln, 2008) and the Santa Barbara Sense of Direction Scale (SBSOD; Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002).

#### 2.4 Forgetting Tests

#### 2.4.1 Task Characteristics

#### 2.4.1.1 Nature of Material

Two novel verbal and visuospatial measures were developed to assess anterograde forgetting. A story task was used to assess verbal forgetting, because prose tasks have greater ecological validity than word list tasks (Baddeley, Rawlings, & Hayes, 2013; Butler & Zeman, 2008b). Similarly, we developed a route video task to assess visuospatial memory, because similar tasks have been shown to have greater ecological validity than pen-and-paper visual memory measures (Barbeau et al., 2006; Tramoni et al., 2011). It has also been suggested that route-task performance is correlated with patients' subjective memory complaints, and thus may be useful in clinical assessment (Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012).

#### 2.4.1.2 Nature of Retrieval

We assessed the story task by cued recall because this enables a greater degree of control over responses than traditional free recall. It has also been shown to offer greater sensitivity than recognition memory tasks (Baddeley et al., 2013). We did not test both recall and recognition conditions because of the difficulty in measuring both these facets on a single task whilst simultaneously avoiding ceiling and floor effects. However, because making a spatial decision typically involves a forced choice decision from a number of options, we assessed recall on the route task both by a series of twooption forced-choice spatial decisions and, in addition, by cued recall of landmarks passed in the video (after each spatial decision).

#### 2.4.1.3 Timeframe of Assessment

In order to make inferences about the timeframe of forgetting, we assessed recall at four intervals. Initial learning was assessed after a 30-second interval, during which a distractor task was performed, in order to eliminate any short-term memory effects (Cowan, 1993; Green & Kopelman, 2002; Isaac & Mayes, 1999a, 1999b; Kopelman & Stanhope, 1997). A 10-minute delay was chosen as the next delay interval because this interval has been shown to be sensitive in detecting differences in initial retention rates (Christensen, Kopelman, Stanhope, Lorentz, & Owen, 1998; Isaac & Mayes, 1999a, 1999b; Kopelman & Stanhope, 1997). We then assessed longer-term recall after one day and then after a week, because these are delay periods commonly used in long-term forgetting research in epilepsy whilst minimising the potential for floor performance (Kemp et al., 2012; Manes et al., 2005).

#### 2.4.2 Story Task

#### 2.4.2.1 Story Task Development

Four story forms were created to assess recall at each of the four delay intervals. Parallel forms were created to avoid repeated recall and subsequent potential reencoding of material (Karpicke & Roediger, 2008; Roediger & Karpicke, 2006). In a first phase of piloting, stories containing 13 units of information and 10 cued recall questions were developed (see Supplementary Material for an example of a story trial). These were to be presented in chronological order, and designed so that earlier answers did not cue later responses within the sequence.

In a second phase of piloting, story trials were matched for difficulty at the 30second delay, and ceiling effects were avoided. A learning criterion of 60% accuracy was selected for the study on the basis that this represented one standard deviation below the healthy participants' mean performance.

#### 2.4.2.2 Story Task Procedure

Participants heard each story on a laptop computer recording. After presentation of the first story, participants completed a distractor task for 30 seconds (subtracting serial 3s from 100) before being asked the 10 cued-recall questions related to that story trial. Using the 60% criterion, learning was matched on a case-by-case basis: if a participant did not reach this criterion at the 30-second delay interval, the story was represented, and cued recall tested again, until this criterion was reached. Having determined the number of presentations needed to reach the 30-second criterion, this number of presentations was used for the remaining stories, which were tested at 10 minutes, one day, and one week after learning. Story allocation to interval condition was counterbalanced using a Latin square design. During the 10-minute delay period, participants completed background neuropsychological tests and questionnaires (NART, and/or EMQ-R, SBSOD). At the one-day and one-week tests, participants received pre-arranged telephone calls, and were then asked cued recall questions about the respective stories. Participants were asked not to rehearse the story during these intervals.

#### 2.4.3 Route Task

#### 2.4.3.1 Route Task Development

The visuospatial task comprised four routes filmed from the front of a moving car using a GoPro fish-eye camera. Modifications were made to the video clips such that the film was paused at spatial decision points and at salient landmarks in the environment during presentation. The landmarks followed immediately after the decision points. Each trial consisted of five spatial decision and five landmark points.

At testing, 'stills' of each of the five spatial decision points were shown in sequential order. Each still had two numbers superimposed on the picture indicating the possible directions the car might drive from that point. This gave a two-option forced choice recognition test. For the 'landmark' task, another still was shown of the same image but without the superimposed numbers. A cued recall question was then asked about the landmark (Figure 1).

Piloting ensured this approach was feasible, that each trial was equivalent in difficulty at the 30-second delay interval, and that ceiling effects were avoided. An 80% learning criterion was selected on the basis that this cut-off represented one standard deviation below healthy participants' mean performance in the pilot study.

\*\*\*\*Insert Figure 1 around here\*\*\*\*

#### 2.4.3.2 Route Task Procedure

During presentation, participants were told that a video of a car driving through a town would be shown, played on a laptop computer. They were asked to imagine being a passenger in the car, and to pay attention to where they went and landmarks passed. The video was paused at different points and their attention was drawn to specific items to remember. Immediately after the first trial, participants completed a distractor task for 30 seconds (separating two steel links in a puzzle), before being asked recall questions corresponding to that trial. If a participant did not reach 80% accuracy, presentation and recall questioning was repeated until this criterion was reached or until they received two presentations of material. Having established the number of presentations needed, this number was used for presentation of the other three filmclips, for 10-minute, one-day, and one-week recall, which were counter-balanced for allocation to the test delays according to a Latin square design. During the 10-minute

recall interval, background neuropsychological assessment measures were completed (GNT, and/or EMQ-R, SBSOD). For one-day and one-week recall tests, participants were told not to visualise or rehearse the route. Participants were emailed a password-protected file containing the stills for these trials, which they accessed on their home computer during testing over the telephone.

#### 2.5 Test Scoring

Each trial for both the story and route tasks was scored out of 20 (see Supplementary Materials for an example of how these tasks were scored). Percentage total recall scores were calculated at each delay interval. These were used to determine forgetting rates in terms of group by delay interaction analyses. For secondary analyses, forgetting rate difference scores were calculated using the formula: (recall at first delay score [i.e. 30-second] – recall score at later delay [e.g. one-week]) / (recall at first delay score [i.e. 30-second]) x 100.

#### 2.6 Statistical Analysis

All statistical analyses were carried out using SPSS. Data was checked for normality (using box plots, Q-Q plots, and the Shapiro-Wilks test) and homogeneity of variance (using Levene's test and Mauchley's test of sphericity as appropriate). Background test scores were compared using t-tests or Mann-Whitney-U as appropriate. Overall analyses and interaction effects were examined using mixed ANOVAs with significance levels set at alpha  $\leq$  .05. Planned comparisons were corrected using Benjamini and Hochberg's (1995) False Discovery Rate. Effect sizes were calculated using Cohen's (1992) *d*. In the comparison of subgroups, forgetting rate difference scores (calculated as above) were checked for normality and then compared using one-way ANOVAs with

t-tests of significant results corrected for multiple comparisons as above. Where the assumption for homogeneity of variance was not met, *Welch's F* ratio was used and t-tests analysed on the assumption of unequal variance (Field, 2013).

#### 3. Results

#### 3.1 Neuropsychological Profile

The patient and control groups were matched for gender, age and educational level (Table 3). There were no differences between groups concerning intellectual functioning, memory, executive and language functioning (all p > .05). The TLE group reported more symptoms of depression (BDI-II: U = 81.50, p = .010), greater subjective everyday memory problems (EMQ-R: t[34] = 3.76, p = .001), and worse spatial navigation abilities (SBSOD: t[34] = -3.39, p = .002).

Table 3. TLE and control participants' demographics and performance on standardised

neuropsychologic	ical tests
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	TLE		Cont	trols	р
	Mean	S.D.	Mean	S.D.	•
Demographic Variables					
Male : Female	9:9		9:9		1.00
Age (years)	39.33	9.80	39.67	13.27	.932
Education (years)	15.06	2.84	15.00	2.97	.955
Cognitive Variables					,
Estimated Intelligence (NART-R)	108.50	10.08	106.39	9.36	.519
Intelligence (WASI-II FSIQ-2)	107.78	13.21	106.00	9.91	.651
Memory (WMS-III)					
Word Lists Learning (WL-I)	32.39	7.04	34.89	4.65	.217
Word Lists Delayed Recall (WL-II)	6.78	3.54	8.39	2.28	.114
Visual Reproduction Learning (VR-I)	83.22	14.13	86.39	15.43	.525
Visual Reproduction Delayed Recall (VR-II)	59.83	29.00	67.22	20.36	.382
Executive Functioning					
Hayling Composite	17.89	2.40	19.17	1.04	.118
Brixton	14.89	7.88	12.28	5.93	.269
Object Naming (GNT)	20.22	5.14	19.22	3.49	.499
Questionnaire Measures					
Depression (BDI-II)	13.94	11.33	4.89	6.90	.010*
Anxiety (BAI)	9.44	11.81	6.17	6.25	.864
Everyday Memory Problems (EMQ-R)	26.89	16.47	11.22	6.45	.001*
Spatial Navigation (SBSOD)	51.67	19.32	70.83	14.27	.002*
*Significantly different (p<0.05)					

#### 3.2 Story and Route Forgetting Tasks

## 3.2.1 Performance Matching at the 30-Second Delay

For both story and route memory, after manipulation of the number of presentations, the patient and control groups did not differ significantly in performance at 30 seconds, stories: t(34) = .282, p = .780; routes: t(34) = -1.705, p = .097. Even so, more participants with TLE required multiple presentations of both verbal and visuospatial material to reach learning criteria: six TLE participants required two presentations of story material vs. no control participant needing more than one; similarly, three TLE participants required two presentations of route material vs. one control participant.

#### 3.2.2 Ceiling and Floor Effects

One-sample t-tests were used to determine whether the patients' and controls' scores differed significantly from ceiling (100%) at 30-seconds, and from floor (0% on the story task and 25% on the route task) at one-week. Floor was 25% on the route task because half the questions involved a two-option forced-choice decision (about direction) and half were cued recall (about landmarks). Table 4 shows that ceiling and floor effects were avoided in both groups on both tasks.

		One-Sample t test			
		<i>t</i> (17)	р		
Ceiling a	at 30 Seconds				
Story	TLE	-6.351	<.001		
	Controls	-7.261	<.001		
Route	TLE	-6.168	<.001		
	Controls	-4.461	<.001		
Floor at	1 Week				
Story	TLE	6.016	<.001		
	Controls	7.498	<.001		
Route	TLE	3.198	.005		
	Controls	5.712	<.001		

Table 4. Examination of ceiling and floor effects

### 3.2.3 Forgetting Effects

Figure 2a shows the forgetting curves on the verbal (story) task. It indicates that the TLE group appeared to forget the story material progressively faster than the control group over the course of one week. A mixed-model two-way ANOVA was used to assess statistical significance: group as the between-subjects factor (TLE and control) and delay as the within-subjects factor (30-second, 10-minute, one-day and one-week). This showed a significant main effect of group, F(1,34) = 6.782, p = .014, and delay, F(3,102) = 99.671, p < .001, and a significant delay-by-group interaction, F(3,102) = 2.929, p = .037. Analysis of paired contrasts revealed only one significant interaction: between 30-second and one-week delay, F(1,34) = 9.396, p = .004. This indicates that,

although participants with TLE appeared to forget the stories progressively faster than control participants, this deviation only became statistically significant at one week post-learning.

Figure 2b shows forgetting curves for the visuospatial (route) task. On this, participants with TLE appeared to forget faster than controls between 30 seconds and 10 minutes, with comparable forgetting rates beyond this delay. An overall ANOVA indicated a significant main effect of group, F(1,34) = 18.374, p < .001 and delay, F(3,102) = 68.601, p < .001, but no significant delay-by-group interaction, F(3,102) = 1.655, p = .182. Although this interaction was not significant, planned comparisons of paired contrasts after learning revealed a significant interaction between 30-second and 10-minute recall, F(1,34) = 7.253, p = .011. The paired contrast interaction from 10-minute to one-week recall was not significant, F(1,34) = .001, p = .973. This suggests that participants with TLE forgot route material at an accelerated rate only between 30 seconds and 10 minutes after learning, with comparable forgetting rates thereafter.

\*\*\*\*Insert Figure 2 around here\*\*\*\*

#### 3.3 Analyses of Epilepsy-Related Variables and Forgetting

Participants with TLE were categorised into sub-groups based on (1) EEG laterality of seizure focus, (2) the presence of medial temporal lobe sclerosis (MTS) on MRI, (3) seizure activity during the week of the experiment, and (4) dosage of anti-epileptic medication. Figure 3 shows performance on the story and route tasks in these subgroups expressed in terms of difference scores.

#### 3.3.1 Laterality of Seizure Focus

Six participants with left TLE and six participants with right TLE were compared with control participants. These subgroups were comparable on all demographic and cognitive variables (all p > .05).

For story memory, performance was not statistically different between groups at 30-second recall, F(2,27) = .341, p = .741. Figure 3a shows both TLE groups forgot more than controls over the course of a week. Laterality of seizure focus was not statistically associated with differences in forgetting rates between 30-second recall and any later delays (all p > .05).

Likewise, for route memory, performance was not statistically different between groups at 30-second recall, F(2,27) = .734, p = .489. Figure 3b shows that the two TLE subgroups forgot at a similar rate between 30 seconds and one day, at a faster rate than controls, but thereafter the right TLE group appeared to forget faster than the left-sided group. Statistically significant differences in forgetting rates were observed only between the 30-second and one-week delays, F(2,27) = 6.424, p = .005 (all other comparisons p > .05). Right TLE participants showed faster forgetting compared with left TLE, t(10) = -2.539, p = .029, and control participants, t(22) = 3.254, p = .004. Forgetting rates of participants with left TLE did not differ significantly from controls, t(22) = 1.528, p = .141. In summary, participants with right-hemisphere seizures showed faster forgetting of route material over the course of one week, compared with controls and participants with left-hemisphere seizures.

#### 3.3.2 MRI Identified Medial Temporal Lobe Sclerosis

Four participants with TLE showed MTS on MRI scan. These participants were compared with 12 participants with TLE who had 'normal' MRI scans (according to

radiological reports) and controls. These subgroups were comparable on all demographic and cognitive variables (all p > .05).

For story memory, performance was comparable between groups at 30-second delay, F(2,31) = .568, p = .572. Figure 3c shows that participants with MTS exhibited faster forgetting 10 minutes after learning, compared with the other patient group and controls. There was a significant between-group difference in forgetting rate from 30second to 10-minute recall, F(2,31) = 5.354, p = .010. The participants with sclerosis showed faster forgetting compared with participants without sclerosis, t(14) = 2.697, p = .017, and controls, t(20) = 3.350, p = .003. Forgetting rates of participants without sclerosis did not differ from controls, t(28) = .622, p = .539. Over the course of a week (Figure 3c), there was a significant between-group difference in forgetting rate, Welch's F(2,16.84) = 14.214, p < .001. Those with MRI-detectable MTS demonstrated faster forgetting between 30 seconds and a week, compared with those who had 'normal' MRI scans, t(12,05) = 2.954, p = .012, and controls, t(19.28) = 5.221, p < .001 respectively. However, the participants with 'normal' MRI scans also forgot faster than controls over the course of a week, t(27.30) = 2.789, p = .01. In summary, participants with MRI-detectable MTS demonstrated faster forgetting of story material during the first 10 minutes after learning, compared with participants without sclerosis and controls. By one week after learning, both patient groups had forgotten story material at rates in excess of controls and those with MTS continued to forget at a rate faster than those without sclerosis.

For route memory, performance was not statistically different between groups at 30-second delay, F(2,31) = 2.671, p = .085. Figure 3d shows that participants with MTS appeared to forget route material faster than the other two groups between 30 seconds

and 10 minutes. However, this was not reflected in statistical analyses, where no forgetting rate comparison reached statistical significant (all p > .05).

#### 3.3.3 Seizure Activity During Participation Week

Five participants with TLE experienced at least one seizure during the week of participation. Two had experienced at least one seizure by one-day delay and all five experienced at least one seizure between the one-day and one-week delays. These five participants were compared with 13 participants with TLE who did not experience a seizure during their participation week, and with controls. Groups were matched on all demographic and cognitive variables (all p > .05).

For story memory, performance was not statistically different between groups at 30-seconds, F(2,33) = .106, p = .900. Figure 3e shows that both patient groups forgot story material faster than the control group across all delay intervals, but that the rate of forgetting between the two patient groups did not differ. On statistical analyses, the only significant between-group effect across the three groups was in forgetting rates from the 30-second delay to recall at one-week, *Welch's* F(2,11.27) = 6.273, p = .015. As reflected in Figure 3e, the two patient groups' rates of forgetting did not differ, t(5.64) = .307, p = .770, but both subgroups forgot story material faster than controls, t(8.89) = 2.681, p = .025 and t(26.58) = 3.489, p = .002, respectively.

For route memory, performance was comparable between groups at 30-second recall, F(2,33) = 1.684, p = .201. Figure 3f shows that those who had a seizure during the experiment week forgot faster than the controls by 10 minutes, which continued at an accelerated rate through the week. The patient group who did not experience seizures during the participation week also forgot faster than controls over these time-periods, albeit to a lesser extent. However, it was only between 30-second and 10-minute recall

that groups differed, F(2,33) = 4.622, p = .017, and no planned comparisons reached statistical significance (all p > .05).

#### 3.3.4 Anti-Epileptic Medication

Nine participants with TLE were undergoing monotherapy treatment for their epilepsy and eight were prescribed polytherapy. These patient sub-groups were compared with control participants. Groups were matched on demographic variables (all p > .05) but differed on a number of cognitive variables including intelligence, verbal memory, and executive functioning (p < .05). Participants on polytherapy performed worse than controls on measures of verbal memory, t(24) = -2.902, p = .008 and t(24) = -2.960, p = .007 (WMS-III WL-I and WL-II respectively), and worse than those on monotherapy on a measure of intelligence (WASI-II FSIQ-2), t(15) = 3.586, p = .003, and the Brixton test, t(15) = -2.410, p = .029.

Despite these differences, story recall at 30-seconds was comparable between groups, F(2,32) = .502, p = .610. Figure 3g shows that participants on polytherapy started forgetting faster than those on monotherapy and controls by 10 minutes postlearning, although both patient groups forgot at similar accelerated rates by one-week. This pattern was confirmed on statistical analyses: significant between-group differences were observed in the first 10 minutes after learning, F(2,32) = 4.319, p = .022, and between 30-seconds and one-week, *Welch's* F(2,18.11) = 6.800, p = .006. In the first 10 minutes after learning, participants on polytherapy forgot story material faster than those on monotherapy, t(15) = -2.420, p = .029, and controls, t(24) = 2.911, p = .008. By one-week, the patient groups were not statistically different from each other, t(12.12) = .218, p = .831, but both the monotherapy and polytherapy groups differed from controls, t(24.98) = 3.643, p = .001 and t(19.15) = 2.844, p = .01 respectively.

Similarly, for route memory, recall was not statistically different between groups at 30-seconds, F(2,32) = 3.195, p = .054. Figure 3h shows that those on polytherapy forgot route material faster by 10 minutes after learning, and those on monotherapy exhibited a more progressive rate of forgetting compared with controls. Even so, only the difference between 30 seconds and 10-minutes was significant across groups, *Welch's F*(2,12.76) = 4.027, p = .044 but no planned comparisons reached significance after correcting for multiple testing (all p > .03).

\*\*\*\*Insert Figure 3 around here\*\*\*\*

#### 4. Discussion

This study examined: (1) whether patients with TLE demonstrated a faster rate of forgetting compared with matched controls on two novel measures; (2) whether the severity of epilepsy-related variables was associated with forgetting rates; and (3) whether any differences in forgetting rate commenced soon after initial learning, or much later. Our study was designed to follow a number of principles (Elliott et al., 2014; Kopelman & Bright, 2012), which would allow us to explore possible causes of any accelerated forgetting and determine whether our data implicated 'early' or 'late' memory consolidation disruption.

#### 4.1 Did we find evidence of accelerated forgetting in our TLE sample?

We found that participants with TLE showed faster forgetting of story material by one week after initial learning. This forgetting was progressive from 30 seconds onwards, although differences in forgetting rate only became statistically significant after one week. In previous studies of verbal forgetting, most found that statistically significant

accelerated forgetting was observed *before* one week (i.e. Hoefeijzers et al., 2014; Jansari et al., 2010; Mulhert et al., 2010; O'Connor et al., 1997). Even so, Lah et al. (2014) found a pattern of forgetting similar to ours in their sample of TLE participants with 'normal' hippocampi on MRI: there was some initial forgetting in their patient group which became progressively accelerated, and statistically significant, over one week.

With regard to route memory, the overall group by time interaction effect was not statistically significant across the four delay intervals. However, visual inspection and planned comparisons indicated that the patient sample forgot visuospatial material faster by 10 minutes. This suggests that participants with TLE forgot route material more rapidly over this early delay, with comparable forgetting rates thereafter. Wilkinson et al. (2012) found a non-significant trend for faster forgetting in the first hour after learning in patients with TLE and right hippocampal sclerosis, whilst Kemp et al. (2012) found evidence of accelerated forgetting in the first 20 minutes after learning in a patient with TLE. Moreover, the pattern of our findings on visuospatial forgetting are consistent with findings in non-epileptic amnesic patients (including those with temporal lobe pathology), which have shown accelerated forgetting within 10 or 20 minutes, after matching for initial memory performance (Christensen et al., 1998; Green & Kopelman, 2002; Isaac & Mayes, 1999a, 1999b; Kopelman & Stanhope, 1997).

We also note that in other forgetting studies in epilepsy, some did not find statistically significant accelerated forgetting (Davidson, Dorris, O'Regan, & Zuberi, 2007; Mulhert et al., 2011; Narayanan et al., 2012) and others only observed accelerated forgetting after longer delays (Evans et al., 2014; Tramoni et al., 2011). Whilst heterogeneity of method and materials are likely to have contributed to the variability of

these findings, there still appeared to be a pattern of progressively faster forgetting in the epilepsy group that either did or did not become significant over time.

# 4.2 Why was there a different pattern between verbal and visuospatial forgetting?

As noted above, faster forgetting on the visuospatial task appeared to occur within the first 10 minutes, but, on the verbal task, differences in forgetting only became statistically significant at one week. Other authors have obtained related findings in TLE patients and Amlerova et al. (2012) noted that this patient group can be at risk of spatial memory impairments. Dewar et al. (2015) reported that transient epileptic amnesia patients demonstrated impaired picture recognition five minutes after learning, despite this sample not exhibiting accelerated forgetting on a verbal task until hours after learning (Hoefeijzers et al., 2014). Additionally, Mulhert et al. (2011) showed that TLE patients were impaired on a spatial recall task at 40-second recall, despite normal performance on all other verbal and visual measures.

In the present study, our route task relied heavily on specific processes associated with three-dimensional spatial navigational skills (Morris & Mayes, 2004), and was selected for its everyday ('ecological') validity. Such spatial navigational processes are known to depend on bilateral interaction between medial temporal lobe structures (Canovas, Leon, Serrano, Roldan, & Cimadevilla, 2011; Glikmann-Johnston et al., 2008), known to be important for 'early' memory consolidation processes (Dudai, 2004). Our patient group also reported significantly poorer spatial navigational abilities, lending further support to the possibility that our visuospatial task may have had greater sensitivity to detect accelerated forgetting within a relatively shorter timeframe compared with our verbal task. Differing task demands and retrieval memory processes

between each measure may have also contributed to differences observed in forgetting rates.

#### 4.3 What variables were associated with accelerating rates of forgetting?

Various pathophysiological variables were also associated with different patterns of forgetting. This was particularly evident on the story task, where both the presence of MTS and anti-epileptic polypharmacy were associated with accelerated forgetting being detectable earlier, i.e., after 10 minutes. Even so, those patients without MTS, and those on monotherapy treatment, still exhibited accelerated forgetting compared to controls but differences in forgetting rate only became significant after one week. The forgetting curve pattern was progressive for those patients without MTS. For those on monotherapy, it appeared to become more divergent (after 10 minutes). Regarding the route task, although the forgetting curves observed were largely similar to those evident on the story task, comparisons did not reach statistical significance.

Others have also found that greater use of anti-epileptic medication may influence forgetting rates at early delays (Butler et al., 2009; Jokeit et al., 2005; Lee, 2010; Motamedi & Meador, 2003; Wilkinson et al., 2012). Similarly, hippocampal sclerosis has been found to influence earlier forgetting (Lah et al., 2014; Wilkinson et al., 2012). Importantly, Lah et al. (2014) found that, of participants with an 'abnormal' hippocampus, most forgetting occurred in the first 24 hours (although they acknowledged that ceiling effects may have masked any forgetting over even earlier delays), whilst those without hippocampal sclerosis exhibited a slower rate of forgetting that only became statistically significant at a week. Further, Wilkinson et al. (2012) compared left- versus right hippocampal sclerosis in TLE patients: participants with left hippocampal sclerosis forgot verbal material faster over a one-hour delay than those

with right hippocampal sclerosis or controls, but both patient groups went on to exhibit faster forgetting by six weeks. The pattern of findings in these studies could, therefore, be seen as broadly consistent with our findings: although MTS may accelerate early forgetting, those patients without sclerosis observable on MRI, still exhibit a slower, more progressive, form of accelerated forgetting.

In the present study, we did not find evidence that seizure activity during the week of testing was associated with accelerating rates of forgetting. This lack of association is similar to some previous research (Blake et al., 2000; Mulhert et al., 2011), but not others (Fitzgerald, Thayer, Mohamed, & Miller, 2013; Mameniskiene et al., 2006; O'Connor et al., 1997; Ricci et al., 2015; Wilkinson et al., 2012). Reasons for this may be related to our measure of seizure activity, which relied on self-report and included any reported manifest epileptiform activity. We were not able to record subclinical activity, timing, or duration of seizures, all of which might contribute to forgetting (Butler et al., 2010). It is possible these variables were influencing the accelerated forgetting rates found in both patient subgroups on our tasks.

Interestingly, the only laterality effect we found was on our visuospatial task: patients with a right-hemisphere origin to their seizures forgot route material over a week more rapidly than left-hemisphere cases (despite the patient subgroups' forgetting curves appearing similar up until one day after learning). There is little other research finding a similar association; the exception being Narayanan et al. (2012), who found a similar trend for faster long-term visual forgetting in those with right-hemisphere TLE by four weeks. However, they did not measure long-term recall at any earlier delay, thus we cannot elucidate whether accelerated forgetting could have been detectable earlier.

In summary, for the story task, it appears that indicators of greater epilepsy severity (i.e. MTS, polypharmacy) resulted in accelerated forgetting that was detectable

earlier, after 10 minutes. The other patient subgroups (i.e. those with 'normal' MRI scans, monopharmacy) still exhibited accelerated forgetting compared to controls, but this was only detectable after a week. Manifest experience of seizures during the participation week did not differentially accelerate forgetting compared to those without seizures. There were similar visual trends on the route task to this effect, but these did not reach statistical significance. Nonetheless, our interpretation must be somewhat tentative, given that the relatively small size of our sample did not permit more rigorous statistical techniques, such as regression analysis, and may also have increased the risk of Type 1 errors. In a sample of 21 patients with TLE, Ricci et al. (2015) argued that only the presence of a hippocampal lesion in TLE patients was predictive of accelerated forgetting (over 24 hours) when all variables were taken into account (such as seizure activity, right-hemisphere involvement, longer duration of epilepsy, greater depression, and hippocampal sclerosis). It will be important for future research in larger series to elucidate further which factors lead to faster or slower memory decay.

# 4.4 What are the implications of our findings for memory consolidation processes?

Our findings implicate 'early' memory consolidation disruption in the phenomenon of accelerated forgetting. Whilst this was particularly evident on the visuospatial task, where forgetting was accelerated in the first 10 minutes after matched learning, the effect of this disruption was more graduated on the verbal task. We therefore posit that faster forgetting in TLE may operate over a continuum of severity (Blake et al., 2000). At one extreme, these 'early' retention deficits are evident soon after learning and could feasibly be detected using adequately sensitive, or 'standard', memory assessment tools. At the other extreme, the deficit is subtler: the rate of faster forgetting is slower, more

progressive, and only becomes statistically detectable after a longer length of time has passed. Various factors, such as task characteristics and greater epilepsy severity (e.g. MTS, polypharmacy), can result in faster forgetting being detected earlier.

This interpretation challenges the position others have made in the field: where statistically significant accelerated forgetting has only been observed after long delays, it has often been concluded these findings result from a disruption to 'late' memory consolidation (Butler et al., 2010; Butler & Zeman, 2008b). However, we found very little evidence to suggest forgetting occurred at 'normal' rates until a later disruption (with only a visual trend of divergent story and route forgetting observed for the monotherapy and right TLE subgroups respectively). Moreover, of the studies listed in Table 1, ceiling effects confounded many of the divergent forgetting curves observed, and approximately half demonstrated a progressively faster forgetting rate in their patient samples, similar to the pattern found on our story task. In summary, our findings challenge the view that memory stabilisation is not disrupted until later delays.

#### 5. Conclusions

We have shown that people with TLE exhibit faster forgetting for both verbal and visuospatial material. This was detectable within 10 minutes of learning on the visuospatial task. On the verbal task, forgetting was slower and more progressive. The difference in this pattern might be related to material sensitivity, and to the particular role of the medial temporal structures in spatial navigation tasks, but might also have reflected other factors as mentioned above.

We have also provided preliminary findings concerning the role of different pathophysiological variables on the timeframe of forgetting. Markers of the severity of epilepsy (the presence of MTS and use of multiple anti-epileptic agents) were

associated with earlier forgetting, at least on our verbal task. Future research will require a larger sample size to examine the relative contribution of these factors to forgetting.

We have argued that our findings implicate the disruption of 'early' memory consolidation processes. The effects of this early disruption can be conceptualised as a 'continuum' of forgetting severity: either apparent immediately or one that becomes more pronounced over time. Whilst we cannot rule out the possibility that memory traces could be disrupted during 'late' consolidation, our data are more consistent with an early retention deficit.

It remains to be demonstrated in patients with temporal lobe lesions whether there is a definite difference between those with or without epilepsy or, for that matter, between TLE and the subgroup with transient epileptic amnesia. Improved understanding of what factors cause and influence rates of forgetting in this population will not only advance our theoretical understanding of memory consolidation, but also aid in the clinical assessment and management of TLE patients reporting concerns with their memory.

#### Acknowledgements

We thank all the participants who participated in this study. We also thank Dr Maria Stefanatou who aided with recruitment and to Daniel Stahl for his advice about statistical analysis.

Professors Michael Kopelman and Robin Morris belong to the NIHR Biomedical Research Centre at King's College London, Institute of Psychiatry, Psychology and Neuroscience. None of the authors have any conflicts of interest to disclose.

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Figure 1. Example of decision-point stills used during route recall trials

Figure 2. Long-term forgetting performance on: (a) story task; (b) route task

Figure 3. Post-learning forgetting rates on: (a) laterality of seizure focus on story task; (b) laterality of seizure focus on route task; (c) medial temporal lobe sclerosis on story task; (d) medial temporal lobe sclerosis on route task; (e) seizure activity during participation week on story task; (f) seizure activity during participation week on route task; (g) dosage of anti-epileptic medication on story task; (h) dosage of anti-epileptic medication on route task





Index: CON, control group; TLE, temporal lobe epilepsy group

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Index: CON, control group; L, left; MT, monotherapy; MTS, medial temporal lobe sclerosis; NSDW, no seizure during week; NMTL, 'normal' medial temporal lobe; PT, polytherapy; R, right; SDW, seizure(s) during week; TLE, temporal lobe epilepsy group