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When "long-term memory" no longer means "forever": Analysis of accelerated long-term forgetting in a patient with temporal lobe epilepsy

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Abstract

Classical amnesia involves a difficulty in transferring information to long-term memory and can be detected with standard clinical tests. However, there are some patients who pass these tests but nonetheless show longer-term memory impairments. A case study is presented of a patient, RY, with temporal lobe epilepsy, who exhibited such a profile of "accelerated long-term forgetting". To investigate the effect of recalling information on later retention, recall and recognition for pairs of novel stories were tested at five intervals ranging from 30 minutes to 4 weeks; we also manipulated whether or not recall and recognition were repeatedly tested for stories. Two studies are reported, one before RY commenced treatment with anticonvulsant medication, and one following 6 months of treatment. Very similar memory profiles were observed in both settings. Against a background of above average cognitive function, results showed that RY's free recall, although initially average or above, was significantly impaired at extended delays (within 24 hours) for non-repeatedly recalled episodic information. However, this contrasted with normal performance for information that had been repeatedly recalled. An unresolved issue in the field is the impact of anticonvulsant medication on alleviating long-term forgetting, and the current study shows that anticonvulsant medication can have negligible beneficial effects in improving the rate of long-term forgetting in this type of patient. In addition, our study highlights the possible protective effect of active review of recent episodic memories.

Keywords: Accelerated long-term forgetting, Long-term amnesia, Temporal lobe epilepsy, Medial temporal lobe, Recollection, Long-term memory

1. Introduction

How does memory for what happened two minutes ago differ from memory for what happened twenty years ago and is there a process that the former undergoes to become the latter? Early functional models of memory suggested a transfer of information from a temporary short-term store to a more long-lasting and possibly permanent long-term one (Atkinson & Schiffrin, 1968). A neurobiological process, consolidation, was postulated to occur at a synaptic level to aid this process (Hebb, 1949). The evidence from studies on patients with selective memory problems (e.g. Scoville & Milner, 1957) supported such a distinction between the two stores or forms of memory, namely short-term memory (STM) and long-term memory (LTM). The major memory impairments of importance, and associated clinical tests, have revolved around intact or impaired STM and intact or impaired LTM.

Recently, however, a number of individual case and group studies have reported patients who pass the standard clinical tests of memory but nonetheless complain of profound long-term memory problems (e.g. Kapur et al., 1996, 1997; O'Connor, Sieggreen, Ahern, Schomer & Mesulam, 1997; Blake, Wroe, Breen & McCarthy, 2000; Mayes et al., 2003; Mameniskiene, Jatuzis, Kaubrys & Budrys, 2006; Butler et al., 2007; Butler et al., 2009). Following presentation of information, such studies have typically tested at 30 minutes (the delay used in most clinical tests), and found no impairment, then tested again at a single long delay of between 24 hours (O'Connor et al., 1997) to 8 weeks (Blake et al., 2000) and found deficits. These studies suggest intact initial acquisition of memories followed by a later accelerated forgetting, though as Butler and Zeman (2008a) point out, the failure to detect any impairment at 30 minutes could also be due to standard tests being insufficiently

sensitive to detect mild deficits in early processing. Although the exact timing of the onset and the progression of the patients' accelerated forgetting is still unclear, this phenomenon of "long-term amnesia" (LTA; Kapur et al., 1997), or "accelerated long-term forgetting" (ALF; Butler & Zeman, 2008a), poses a challenge to the standard clinical measures as well as to the underlying theoretical assumptions. It should be noted that in a review of neuroimaging studies, Gilboa (2004) has suggested that the brain mechanisms for recalling artificial stimuli in the laboratory (and by extrapolation in the clinic) are different from those involved in recollecting personal autobiographical memory. This difference may go some way to explaining the difficulty in capturing levels of real-world accelerated forgetting within the clinic.

Traditionally, information that has been retained for even a few minutes was assumed to have made the transition from short-term or working memory to a long-term store (Parkin, 1993). This view has often made the assumption that this transition involves a single-stage process of consolidation (Weingartner & Parker, 1984). However, evidence from studies of LTA suggests that after the initial 'fixation' of memory within the first 30 minutes, subsequent preservation may require further stages of consolidation before information that is initially encoded and learned is set down in a more permanent store(cf. Frankland and Bontempi, 2005). A failure of these secondary consolidation processes could explain the pattern of accelerated forgetting distinctive to ALF.

Further evidence for secondary consolidation processes comes from the study of retrograde amnesia in cases of medial temporal lobe (MTL) damage. Temporal

gradients in such cases, (which can extend for months or even years (e.g. Zola-Morgan, Squire & Amaral, 1986), with older memories intact while memory for newer pre-morbid material is degraded, suggest that at least some memories are at first reliant on the MTL, but through secondary consolidation become less reliant on this structure over time.

Alvarez and Squire (1994) suggest that information that binds together or indexes the various components of a complete memory is initially stored in the MTL, and then shifts laterally to the neocortex. With this in mind, Mayes et al. (2003) highlight the fact that although reported ALF cases arose from multiple aetiologies (including anoxia, encephalitis and head injuries) either temporal cortex damage or epilepsy (often with a temporal lobe focus), or both, are present in most cases, while damage to the MTL region is rare. They speculate that in ALF the intact MTL allows initial consolidation of binding information, while transfer of this information to, or its maintenance within the long-term storage sites in the neocortex may be impaired. Possible causes they discuss include structural damage to these neocortical sites, failure of the transfer process, failure of maintenance processes that sustain memories in the MTL or neocortex, or disruption of any of these processes by epilepsy. However, as ALF is defined by distinctive abnormal forgetting rather than by any specific anatomical aetiology, it may be that both temporal cortex damage and epilepsy can cause the condition. Butler and Zeman (2008b) report radiological evidence that transient epileptic amnesia (TEA), which is often accompanied by ALF, can be associated with seizure activity in the hippocampus, and in a review (Butler & Zeman, 2008a) of ALF in cases of TEA conclude that both sub-clinical epileptiform activity and structural damage are likely causal factors.

In ALF cases involving epilepsy, a further possible confound is the impact of epilepsy medication. In most or all reported cases patients were under medication at the time of test (e.g. Mayes et al., 2003; Kapur et al., 1996; Mameniskiene, Jatuzis, Kaubrys & Budrys, 2006). While O'Connor et al. (1997) found that anticonvulsant medication improved memory indirectly, through minimising seizures, and Midorikawa and Kawamura (2007) report a case with improvement in ALF under successful anticonvulsant medication, high serum levels of epilepsy drugs have also been shown to impair retention (but not acquisition), of new information (Jokeit, Kramer & Ebner, 2005). Butler and Zeman (2008a) argue that the accelerated forgetting seen in cases of TEA is unlikely to be a direct result of anticonvulsant treatment as patients subjectively report symptoms prior to treatment, and often report improvements after treatment. Theorising about the cause(s) of ALF would be aided by objective studies of ALF in epilepsy cases prior to administration of medication. If combined with comparative testing after treatment commences, such studies would also assist in clarifying the impact of anticonvulsant medication on memory deficits in such cases.

Although the cause of ALF is not yet clear, there is some evidence that rehearsal or repetition can help to counteract its effects. For example, Mayes et al. found that for their patient JL, "greatly over-rehearsed semantic memories were invulnerable to the effects of LTA" (p. 595, 2003). If true for ALF cases in general this has important clinical implications, as it offers the basis for memory strategies to help patients overcome their deficits.

Repetition and rehearsal have been extensively studied within the general cognitive field of memory research and also in memory rehabilitation, and both have been found beneficial in consolidating memories (e.g. Ebbinghaus, 1885; Wilson, Baddeley, Evans & Shiel 1994). However, while these approaches may be useful for learning lists of words or other information which can be re-presented, they are not easily applied to memory for events and episodes in general life, unless these have been recorded in some way (e.g. use of a portable, automatic camera, "SenseCam", Berry et. al., 2007).

Although such repeated recall has not been specifically tested in cases of ALF, there is some general evidence for its benefits. Successful retrieval of an item has been shown to have a positive effect on later ability to recall the same item (Whitten, 1978), sometimes referred to as the retrieval practice effect (Baddeley, 1997), and active recall of material can enhance memory more than a second, passively received, representation of the information (McDaniel & Masson, 1985; Roediger & Karpicke, 2006). Repeated recall at expanding delays, a method referred to as spaced retrieval, has proven successful with dementia patients, amnesics and normal healthy participants (e.g. Landauer & Bjork, 1978; Brush & Camp, 1998; Cull, Shaugnessy & Zechmesiter, 1996). However, it should be noted that spaced retrieval procedures typically include re-presentation after retrieval failure, to maintain performance at ceiling.

It may be that rehearsal, repetition and repeated recall all assist with the postulated MTL to neocortex transfer process. Alternatively they may simply strengthen existing memory traces. It is also postulated by some (e.g. Damasio, 1986) that a

whole new trace is laid down conjointly with a trace that is reactivated (see also the 'multi-trace theory' of Nadel & Moscovitch, 1997).

The current study investigated the impact of repeated recall without re-presentation of novel information on the memory performance of a patient, RY, who exhibited ALF. The time course of the patient's accelerated forgetting was also studied through testing at multiple delays. Two experiments were run, separated by 9 months. As a result of Experiment 1 the patient was referred for neurological investigations and was subsequently diagnosed with temporal lobe epilepsy. Since the Experiment 1 results were obtained prior to this diagnosis and the commencement of anticonvulsant drug treatment, they are free from any drug-related confounds. Experiment 2 was run after 6 months of drug treatment, and we therefore had an ideal opportunity to investigate the impact of anticonvulsant medication on accelerated long-term forgetting.

2. Case History

RY is a right-handed man born in 1939. He currently runs a small web design and software company. RY presented in May 2001, reporting that for about the past year his memory for details of events and images appeared to fade after about 4-6 weeks. For example, a few months after a round-the-world trip, when asked something by his wife about their time in Hawaii, he claimed never to have been there. When looking at photographs of the holiday, these did not bring back any recollections, and social events that he had attended with his wife six months before had been totally forgotten. He occasionally found it a little more difficult to refer back to computer programming work he had done one or two years earlier. He found that he had to

refer to his earlier work and to the computer language much more than he would have done before. Standard neuropsychological testing of current cognitive function identified no deficits and indeed his general memory performance was in the higher ranges (see Table 1). The only exception to this was RY's autobiographical memory. On the AMI (Autobiographical Memory Interview; Kopelman, Wilson & Baddeley, 1990), across all time periods, RY performed in either the 'probably abnormal' or 'definitely abnormal' range. This pattern applied to both the episodic memory and the personal semantic memory subsections. Therefore, RY's current cognitive performance on standard tests appears normal while his remote memory seems poor. Finally, RY reported difficulties in navigating by car to once-familiar locations. He reported that, although he could use various skills such as map-reading to get to a particular place he has been to numerous times in the past, he was no longer able to visually picture the route. At present, however, there is no way to evaluate or quantify this difficulty.

Table 1: Neuropsychological assessment of RY

Table 1

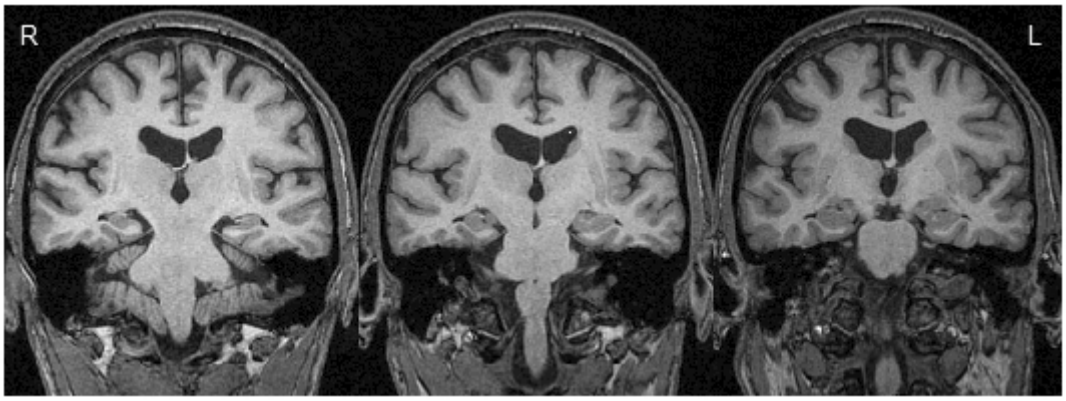
Test	Sub-test	RY's performance
NART (errors = 10)		Pre-morbid IQ 118
WAIS-R	Performance IQ	124
	Verbal IQ	123
WMS-R	Stories Immediate Recall	28 (80th percentile)
	Stories Delayed Recall	25 (82nd percentile)
	Designs Immediate Recall	36 (95th percentile)
	Designs Delayed Recall	34 (94th percentile)
WMS-III	Faces Immediate Retention	41 (scaled score 14)
	Faces Delayed Retention	44 (scaled score 18)
Rey-Osterieth Figure	Delayed visual recall	70th Percentile
WRMT	Faces	67.5th Percentile
	Words	86.7th Percentile
AMI	Childhood semantics	10.5/21 (Definitely abnormal)
	Childhood autobiographical	4/9 (Probably abnormal)
	Early Adulthood semantics	11.5/21 (Definitely abnormal)
	Early Adulthood autobiographical	4/9 (Probably abnormal)
	Recent semantics	15/21 (Definitely abnormal)
	Recent autobiographical	4/9 (Definitely abnormal)
WSCT		6 Categories (Normal)
Graded Naming Test		24/30 (Normal)

WAIS-R= Wechsler Adult Intelligence Scale Revised; WMS-R= Wechsler Memory Scale Revised; WMS-III= Wechsler Memory Scale III; WRMT= Warrington Recognition Memory Test; AMI= Autobiographical Memory Interview; WSCT= Wisconsin Card Sorting Test

Other than cardiac surgery in 2005, RY has an unremarkable medical history. (It is interesting to note that Zeman, Boniface & Hodges (1998) found that a history of cardiac disease was common in their series of patients with TEA.) RY also reported that since childhood he experienced what he referred to as 'turns' where his awareness changes and he feels a sense of déjà vu for about 20 seconds. This feeling of déjà vu is followed by a 'dreamlike' episode which may involve forgotten memories being evoked from the past. Some of these memories can be quite vivid and he usually reports that following the turn, he can remember them but they also

fade rapidly. Although he had experienced episodes as a child, they had become frequent and noticeable just before 2000 and at the time of presentation, were occurring in clusters of four or five episodes about twice a month and usually occurred in the morning after a lack of sleep. These episodes were not associated with any olfactory, gustatory or epigastric sensations. Clinical investigations conducted when RY first complained of memory problems did not find evidence of epilepsy. However, subsequent to the testing in Experiment 1 of the current study - which revealed significant memory problems both on laboratory tasks and autobiographical memory measures - in conjunction with RY's description of his turns and feelings of déjà vu the possibility of subclinical epilepsy was investigated. A sleep-deprived EEG subsequently showed right temporal spike activity (with a greater number of epileptiform discharges occurring while asleep than while awake), and he was given a diagnosis of temporal lobe epilepsy by a consultant neurologist. He has since been prescribed anticonvulsant medication (Lamotrigine, 50mg, twice daily). Neuropsychiatric evaluation performed at diagnosis identified no psychosocial causal factors and MRI investigation in 2007 found no evidence of focal or generalised pathology (Fig. 1). Figure 1 shows three coronal slices through the length of RY's hippocampi, and these images of the hippocampus were judged by two independent experts to be structurally normal.

Fig. 1. T2 weighted 3D coronal images of patient RY showing normal hippocampi bilaterally



3. Experiment 1

3.1 Method

3.1.1 Normal Controls

RY's performance was compared to 8 age- and reading-score derived IQ-matched healthy control subjects who were free of neurological or psychiatric disorders. RY: age at time of testing = 63, NART IQ=118. Control group: N=8; 3 males, 5 females, mean age 66.3, SD 4.9 years, mean NART IQ 117.88, SD 6.29. All participants gave informed written consent to take part in the study, which was approved by the local ethical committee.

3.1.2 Stimuli & Procedure

Participants were tested on recall and recognition of structured prose material using ten stories made up of between 200 and 250 words (Jansari, & Tranel, 1999). Each story (identified by a one-word title, e.g. concert) had been created to include twenty idea units of information to allow free recall to be assessed systematically. Additionally, six three-alternative forced-choice questions were produced for each

story to test recognition ability. During the presentation phase, each story was read out loud by the experimenter with the participant following it on a written copy; following this they were given one additional minute for silent reading. Stories were presented in pairs with each pair being separated by unrelated material or general conversation to avoid confusion. The time delay between successive pairs of stories was usually about ten minutes. It should be noted that the stories were only presented at this one unique time point and never again.

At the point of testing, the participant was presented with the one-word title and asked to recall in as much detail everything they could remember about each story; recall was tape-recorded and later transcribed for scoring. Following free recall, the recognition test for that story was presented. In order to assess the effect of frequent recall on memory performance, participants were required to recall stories 1 & 2 and complete the forced choice recognition (FCR) test at *all* time points (30 minutes, 1 day, 1 week, 2 weeks and 4 weeks). The remaining materials (stories 3–10) were tested for recall and recognition in pairs at one *single* time point only (i.e.. stories 3 & 4 only at 1 day, stories 5 & 6 only at 1 week, stories 7 & 8 only at 2 weeks and stories 9 &10 only at 4 weeks). Figure 2 depicts a schematic of the presentation of pairs of stories on one day, each pair being separated by a break, and then the subsequent testing regime for each pair of stories. Following transcription of the verbal protocols, free recall was scored against the 20-item list of idea units for each individual story.

Table 2: Experiment 1 presentation and testing regime (3AFCR = 3 Alternative Forced Choice Recognition)

Table 2

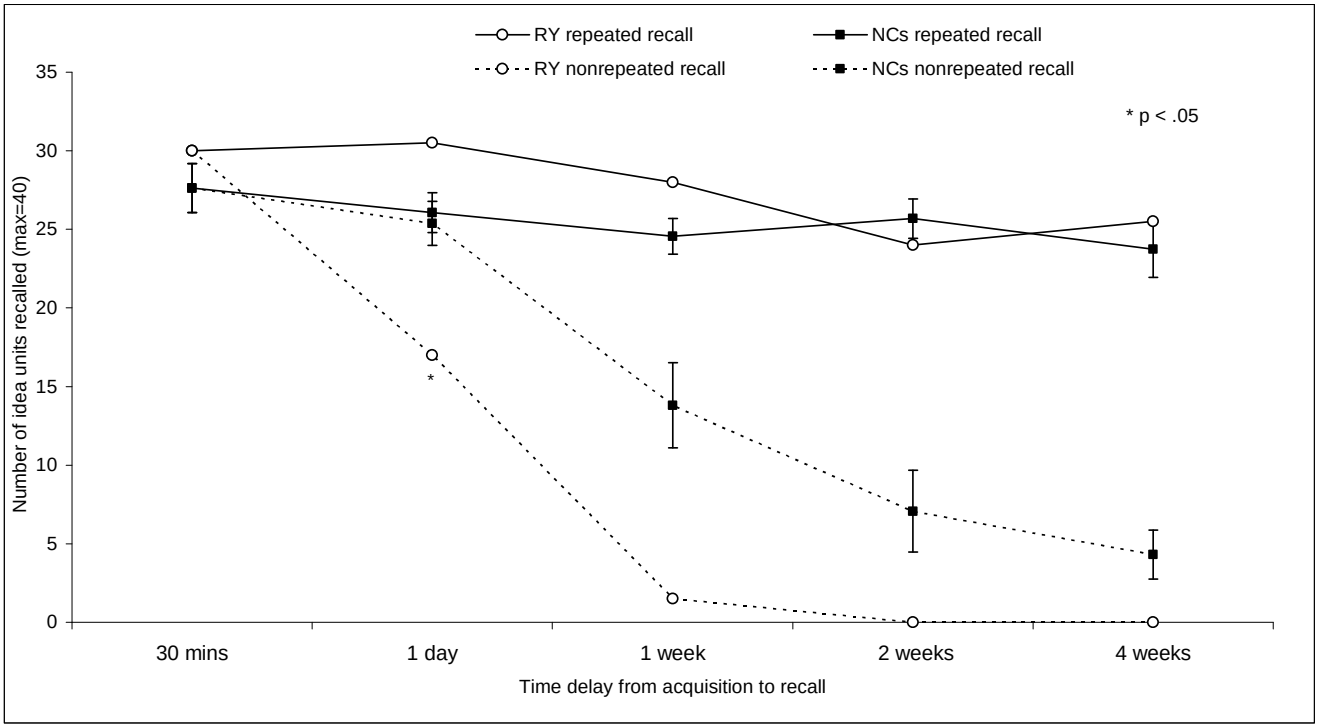
Story pairs	**Testing interval**				
	30 mins	**1 day**	**1 week**	**2 weeks**	**4 weeks**
Story 1 **Story 2**	Free recall & 3AFCR	Free recall & 3AFCR	Free recall & 3AFCR	Free recall & 3AFCR	Free recall & 3AFCR
Story 3 **Story 4**		Free recall & 3AFCR			
Story 5 **Story 6**			Free recall & 3AFCR		
Story 7 **Story 8**				Free recall & 3AFCR	
Story 9 **Story 10**					Free recall & 3AFCR

3.2 Results

For free recall of the repeatedly recalled stories (1 & 2), RY performed similarly to controls (Fig. 2). However, a very different picture emerged when assessing retention of material that was only ever recalled once. Using Crawford & Garthwaite's (2002) method for comparing a single case with a group of control subjects, the free recall scores showed this differing performance most dramatically - RY's recall is significantly impaired by 1 day ($t(7)=1.99$, $p< .05$), at 2 weeks he recalled zero details out of 40, and at the 4 week interval he claimed that he had never seen the stories that he was being tested on. Comparing the performance curves for 'repeatedly recalled' and non-repeatedly recalled' stories in Figure 2 shows the

disparity in RY's pattern of retention between the two types of information and clearly demonstrates a reinforcement effect for repeatedly recalled material[1].

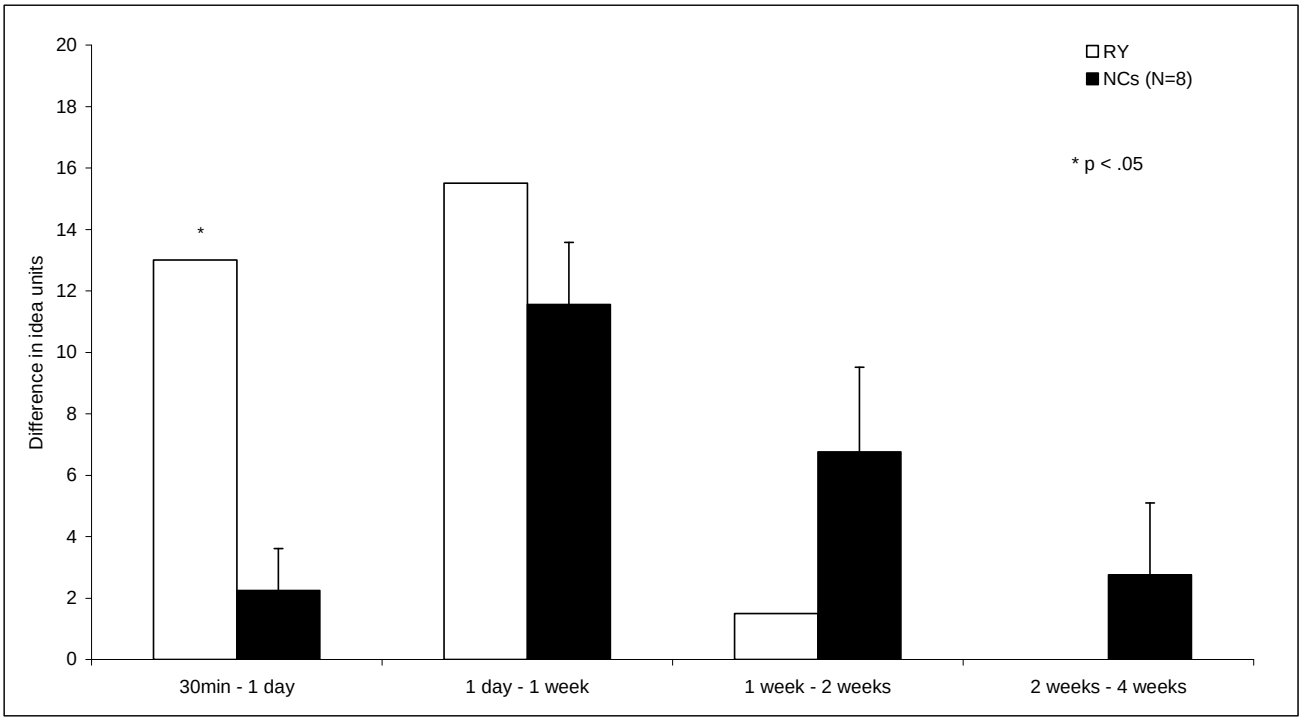
Fig. 2. Free-recall of stories in Experiment 1 (error bars represent one standard error)



Given that RY displays accelerated forgetting for the non-repeatedly recalled stories, the timeframe of this forgetting was analysed by exploring the loss of information between consecutive recall sessions. For each participant, the difference in free recall scores between adjacent timepoints was computed (Fig. 3). Analysis of this forgetting data showed that RY lost significantly more information than controls between 30 minutes and 1 day ($t(7)=2.63$, $p<.05$), confirming that his accelerated forgetting starts within the first 24 hours.

[1] Please note that the first data point for the non-repeatedly recalled series is the first recall of Stories 1 & 2 since at this point they have not been recalled before. As they are then subsequently recalled at

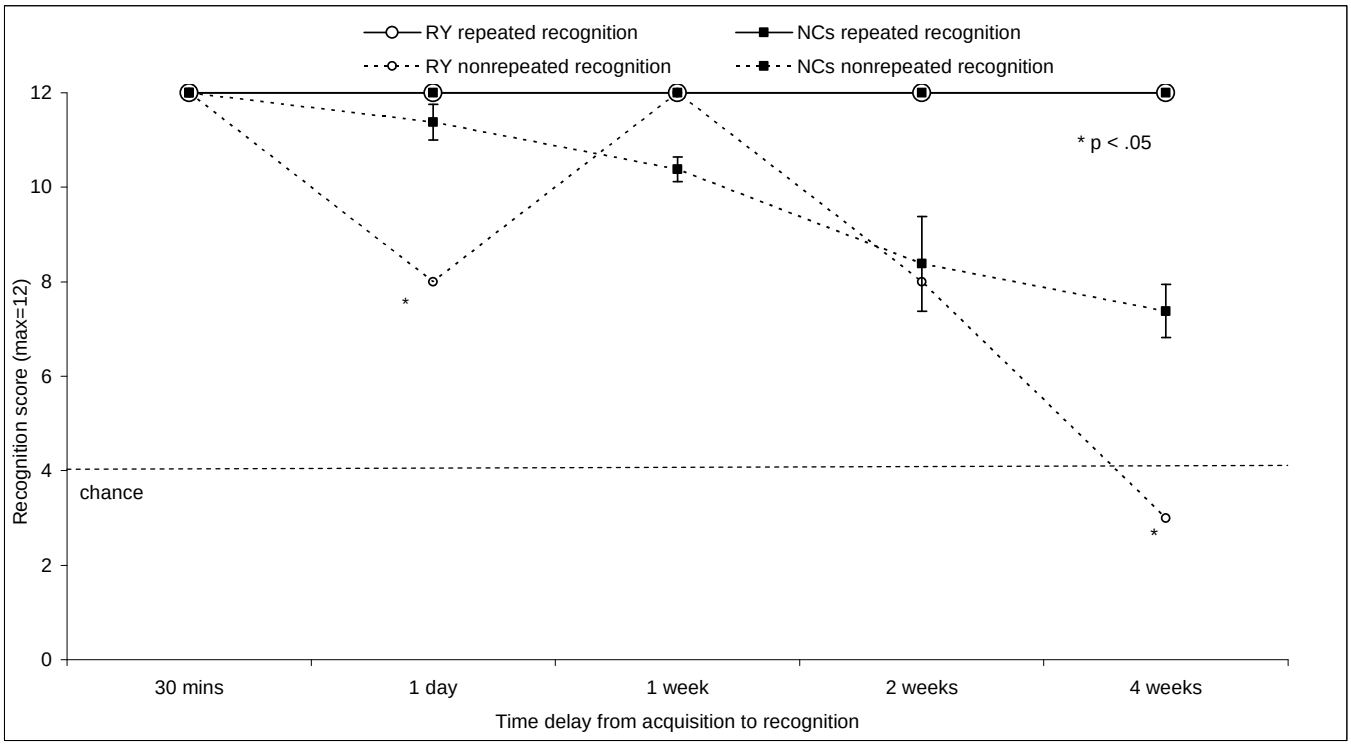
Fig. 3. Reduction in free-recall performance between test intervals in Experiment 1 (error bars represent one standard error)



Recognition for information from the repeatedly recalled stories was at ceiling (a maximum score of 12) for both RY and all controls at all time points (Fig. 4). In contrast, RY's performance for recognition of the non-repeatedly recalled information was variable. He was impaired for the 1 day stories ($t(7)=3.01$, $p<.05$), and for the 4 week stories ($t(7)=2.58$, $p<.05$) for which he performed below chance.

every time point, they also form the first data point for the repeatedly-recalled series.

Fig. 4. Recognition of stories in Experiment 1 (error bars represent one standard error)



3.3 Discussion of Experiment 1

Standardized neuropsychological tests showed that RY performed normally, or in the above average range for his age, indicating no impairment in general cognitive function or in the acquisition of new memories. However, detailed testing designed to assess specific aspects of RY's behavioural, as opposed to clinical profile, showed a rather different picture. If allowed to recall information repeatedly, RY shows normal performance certainly within the timeframe of the current study. In contrast to this, for matched material that he is not allowed to repeatedly recall, RY's free recall performance begins to diverge from that of controls within one day of initially learning the material. At 4 weeks, he has effectively reached amnesic levels, which

reflects his and his wife's anecdotal report of the time-frame of his memory loss. Thus RY's memory profile for non-repeatedly recalled information was found to reflect that of other ALF patients (Ahern et al., 1994; De Renzi & Lucchelli, 1993; Kapur et al., 1996; Lucchelli & Spinnler, 1998; O'Connor et al., 1997; Mayes et al., 2003; Butler et al., 2008; Butler et al., 2009), where memory for episodic information is initially preserved, but then found to be impaired at longer time intervals.

Shortly before RY's tests of recall and recognition at the 1 day time interval, RY reported having what he referred to as 'a mild turn' and performed significantly below the control group for the recognition of the non-repeatedly recalled material. However, he then performed better than controls at the subsequent 1-week interval (see Fig. 4). This pattern of performance, however, appeared to be restricted to this one test, indicating possible interference with memory retrieval rather than with memory loss (due to the recovery of his performance at 1 week), as RY's free recall of non-repeatedly recalled material, although equally impaired at the 1 day interval, continued to fall beyond this time point (no recovery; see Fig. 2). However, it is also possible that the turn impacted both recall and recognition for the non-repeatedly recalled information tested at the 1day interval and that if it had not occurred, RY's memory at this point would have been within normal limits. Any accelerated forgetting might then only have become visible at or after the 1 week testing point. This possibility is addressed in the light of the findings from Experiment 2 below.

4. Experiment 2

Experiment 2 was a partial replication of Experiment 1, performed after RY had been taking medication for 6 months (see Case History), and was intended to identify any changes in RY's ALF as a result of the medication. At this time RY reported that he had been seizure-free since commencing drug treatment. If RY's ALF is directly due to seizures, and if the medication did successfully eliminate or greatly reduce seizure occurrence, then an improvement in his memory would be predicted.

4.1 Method

4.1.1 Normal Controls

RY's performance was compared to a new group of 6 age, sex and IQ-matched control subjects who were free of neurological or psychiatric disorders (mean age, 61.83, SD 5.41 years, mean NART IQ 122, SD 5.79). All participants gave informed written consent to take part in the study, which was approved by the local ethical committee.

4.1.2 Stimuli & Procedure

Eight new stories made up of between 200 and 250 words (based on the format used by Jansari, & Tranel, 1999) were prepared. Presentation and test procedures were identical to Study 1 with two exceptions.

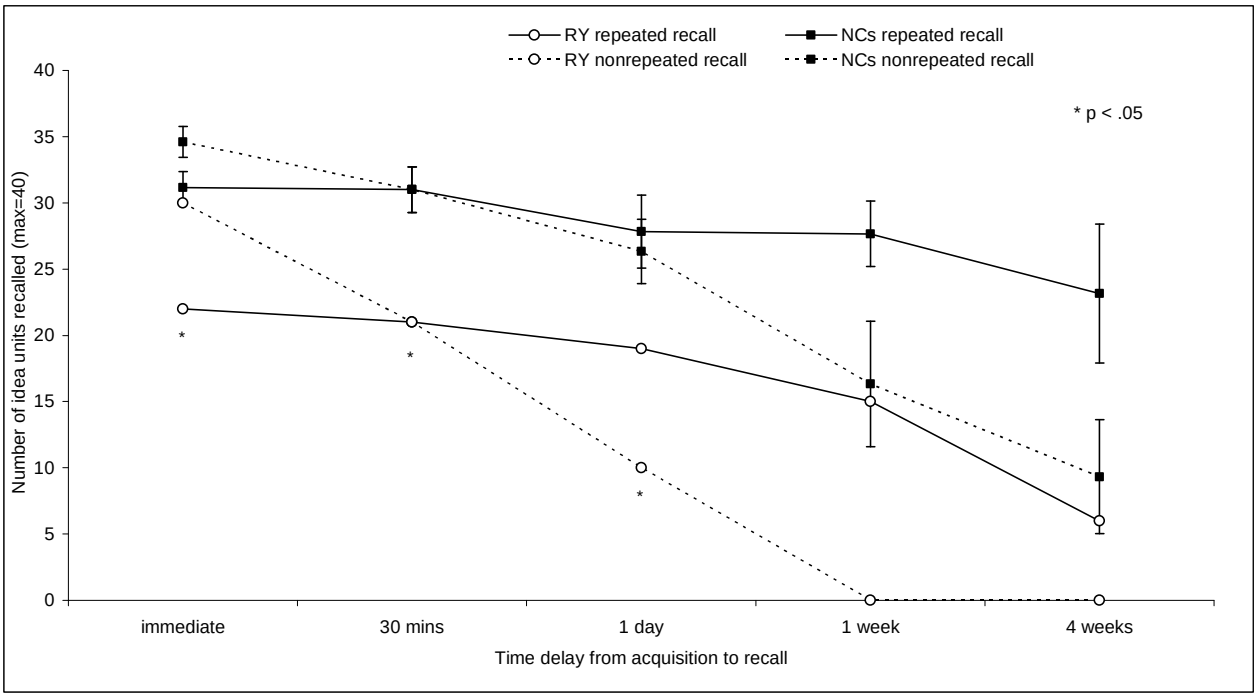
Firstly, the participant recalled each story immediately upon completion of the presentation phase. The resulting immediate recall score shows how much of the

material had been successfully encoded, and therefore any subsequent forgetting was of already-encoded material. Secondly, given RY's equally poor performance at two and four weeks in Experiment 1, it was felt that testing at both intervals was unnecessary, and it was therefore decided to omit the two week test point.

4.2 Results

Initial encoding was evaluated by analysing the immediate recall of the stories. This revealed that RY's immediate recall across all eight stories was impaired relative to the controls ($t(5)=2.11$, $p=0.04$); further analysis revealed that this immediate recall was significantly impaired for story pairs 1 & 2 ($t(5)=2.90$, $p=0.02$) which were later repeatedly recalled. Figure 5 shows immediate and then subsequent recall of the eight stories; note that the immediate recall score for the non-repeatedly recalled stories is the average of all six stories with subsequent data points showing the recall of individual pairs of stories. Unlike Experiment 1, RY's free recall of the repeatedly recalled stories (1 & 2) was impaired at the 30min interval ($t(5)=2.21$, $p=0.04$) but thereafter was within normal limits at all subsequent time points; this issue is addressed in the Discussion of Experiment 2 and the General Discussion. However, as in Experiment 1, a different picture emerged when assessing free recall of non-repeatedly recalled material. In line with Experiment 1, RY's performance for free recall of this material was significantly impaired by the 1day interval ($t(5)=2.54$, $p=.03$), and was at floor by 1 week.

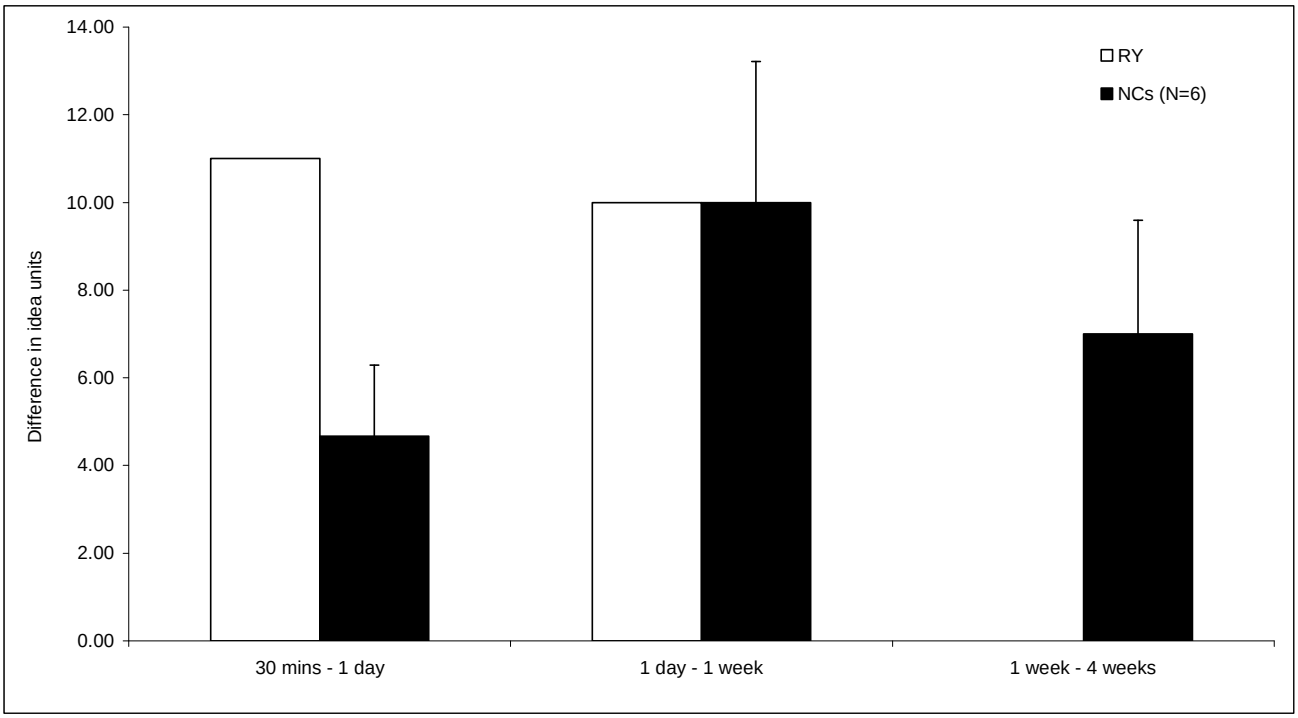
Fig. 5. Free-recall of stories in Experiment 2 (error bars represent one standard error). The immediate recall for the non-repeatedly recalled stories is based on the average of all three pairs of stories which were then only recalled at one unique timepoint.



Comparing the curves for recall of 'repeatedly recalled' and non-repeatedly recalled' information in Figure 5 shows the disparity in RY's pattern of retention of the two types of information and again demonstrates a reinforcement effect for repeatedly recalled material. To further explore the rate of memory deterioration, the information loss between consecutive recall sessions for the non-repeatedly recalled stories was computed for each participant (Figure 6). In common with Experiment 1, this analysis showed that RY lost substantially more information than controls between 30 minutes and 1 day; there was a trend towards significance for his forgetting rate being worse than that of the controls but it did not reach conventional

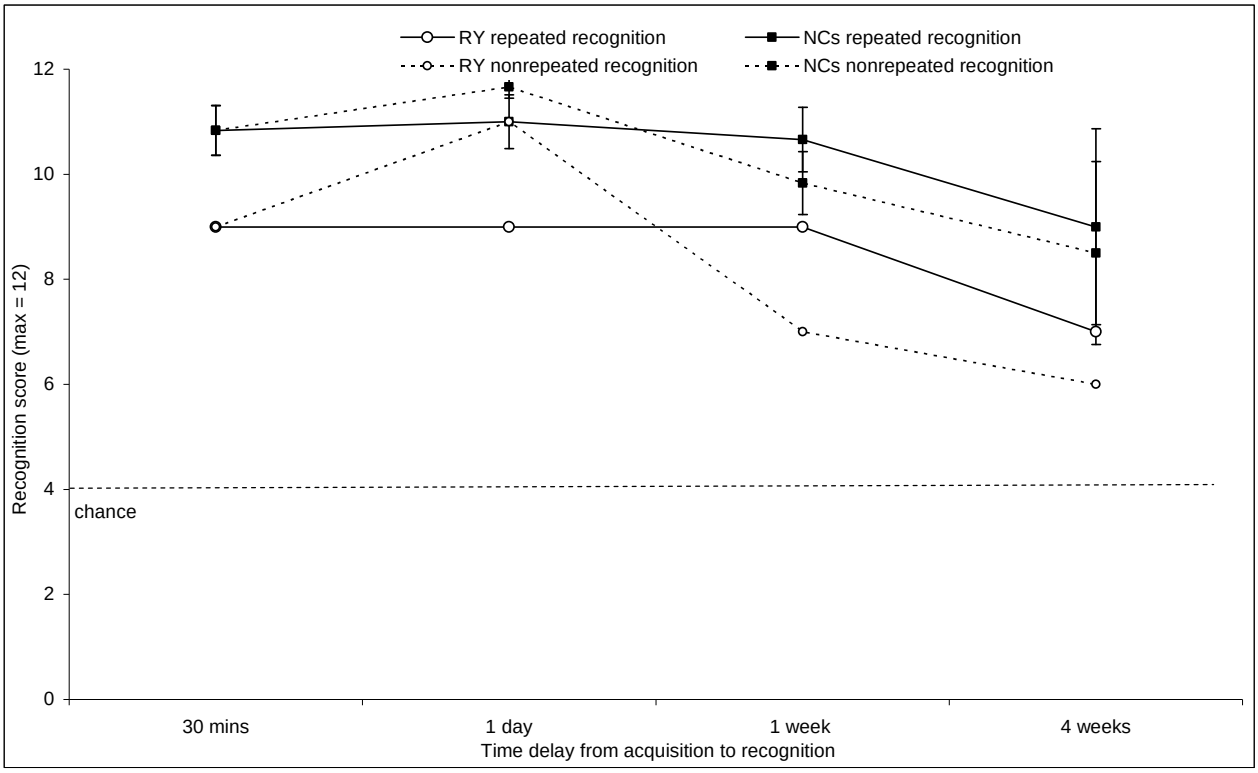
significance levels (t(5)=1.47, p=0.10). This adds support to the suggestion that RY's forgetting begins within the first 24 hours.

Fig. 6. Reduction in free-recall performance between test intervals in Experiment 2 (error bars represent one standard error)



For recognition of information from the repeatedly recalled stories, although RY's performance was slightly lower than the controls, he was within normal limits (Figure 7). RY's performance for nonrepeatedly recalled material was also slightly lower than controls, though not significantly so, and his forgetting rate was again in line with the control group. This performance differed from Experiment 1 in which he was below chance at the longest interval.

Fig. 7. Recognition of stories in Experiment 2 (error bars represent one standard error)



4.3 Discussion of Experiment 2

Experiment 2 was intended to identify any changes in RY's ALF as a result of 6 months of treatment with anticonvulsant medication; one prediction would have been that controlling his epilepsy would improve his memory. Surprisingly, by measuring immediate recall, it was seen that RY's initial encoding was worse than that of matched healthy controls. This could be a direct consequence of the adverse effects of anticonvulsant medication on memory functioning (Meador, 2006; Motamedi & Meador, 2004). Following initial learning, as in Experiment 1, if RY is only allowed to recall information at one unique timepoint, his memory is already impaired within

1 day and rapidly falls to the floor thereafter. As stated in the Discussion of Experiment 1, the turn that RY experienced at the 1 day testing meant that it was not possible to state unequivocally that his accelerated forgetting started within the first 24hrs since it could have contributed to both his poor recall and recognition of the non-repeatedly recalled material. However, in the absence of any turns being reported during Experiment 2, the rapid forgetting that occurred for equivalent material strongly suggests that indeed, the rapid forgetting is beginning this early[2]. In contrast, and echoing the findings of Experiment 1, repeated recall has a beneficial impact. RY's initial (immediate) recall of the first two stories was significantly worse than that of the controls and this probably contributed to his poorer performance when recalling these stories 30 minutes later. However, despite this 'poor start', repeated recall then brings his memory within normal limits and although his memory is never the same as that of controls, there is no catastrophic forgetting to floor levels within a week as there is for the non-repeatedly recalled stories.

In Experiment 1 recognition of non-repeatedly recalled information matched controls at 2 weeks, but then fell to chance by 4 weeks, reflecting an accelerated forgetting. In Experiment 2, however, recognition for this material type was maintained within normal levels at all intervals. This appears to indicate an improvement in recognition memory.

[2] It should be noted that although the difference in the forgetting rates for the first 24hrs shown by RY and the matched controls did not reach significance (Fig 6), this was most likely driven by the poor recall of the stories tested at 30mins reducing the absolute level of forgetting from that point to the 1 day testing period. Since the poor recall was itself probably driven by weak initial encoding of these stories, our speculation is that this in fact contributed to the lack of a significant effect. Indeed, in an analysis not presented here, where recall was measured as a proportion of initial encoding, RY's recall

Relative to Experiment 1, there thus appears to have been no improvement in RY's free recall, and some improvement in recognition memory; this is coupled with impaired initial encoding of material which was not evaluated in Experiment 1. This is a complex picture and addressed in the General Discussion.

5. General Discussion

This study has identified a further case of accelerated long-term forgetting (ALF), thus confirming again the existence of patients who can pass all standard clinical memory tests, yet still suffer from significant long-term memory deficits. In this case the patient, RY, displays normal memory performance at 30 minutes, but significantly degraded free recall of non-repeatedly recalled episodic information after 1 day. Using a new paradigm comparing the impact of repeatedly recalling the same information against recalling information only at one unique timepoint, it was possible to show that the former can have a protective effect on memory traces. If this does not happen, the patient's memory for novel information falls to floor levels within two weeks. Finally, because the patient had not been given a diagnosis of epilepsy before the research began and only received one after the completion of Experiment 1, it was possible to evaluate the impact of anti-epileptic medication by testing him before and after six months of drug treatment. While recognition memory seemed better, no overall improvement in free recall was found following medication.

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at 30mins was within normal limits and his forgetting rate within the first 24hrs was significantly impaired relative to controls replicating the findings of Experiment 1.

ALF has been found to have a close association with temporal lobe epilepsy generally (TLE; e.g. Blake et al., 2000; Martin et al., 1991) and with a specific type of TLE known as transient epileptic amnesia (TEA; e.g. Butler et al., 2007). Both TLE and TEA patients often report persistent memory problems (e.g. Baxendale et al., 1998; Mameniskiene, Jatuzis, Kaubrys & Budrys, 2006; Butler et al., 2007). Accelerated forgetting has also been identified for material learnt shortly after electroconvulsive therapy (ECT) for depression, suggesting that transient impairment of neuronal function may disrupt consolidation (Squire, 1981; Lewis & Kopelman, 1998). It is therefore possible that epileptiform activity interferes with secondary (slow) processes of memory consolidation. One confound in previous TLE and TEA studies, however, is that patients were taking anticonvulsant medication at the time of testing. Therefore, there is a possibility that the medication may have contributed to the observed memory deficits. Although O'Connor et al. (1997) identified the presence of accelerated forgetting in a single case study prior to administration of drugs, the patient in question was experiencing a high seizure rate (20-30 per day even with medication), and a single control subject was used for comparison. Midorikawa and Kawamura (2007) found evidence of improvement in ALF under successful medication by checking memory for events occurring before and after start of medication. However, memory testing could not be performed prior to medication for ethical reasons, and their study did not control for encoding level. The current study included a group of matched controls, and a paradigm suited to testing episodic memory (free recall of short stories). To our knowledge the current study is therefore the first to unequivocally demonstrate ALF in a patient who was drug free, and therefore show that any amnestic effect of anticonvulsant drugs cannot be the sole cause of ALF.

As RY has reported experiencing ‘turns’ since childhood and has only reported memory problems in the last decade, any direct connection between the frequency of epileptiform activity and his memory loss remains unclear. However, there is little evidence as yet that points to other sources of pathology that could account for his memory impairment. A lack of any obvious pathology has been reported in other ALF cases (e.g. Lucchelli & Spinnler, 1998), and although Butler et al. (2009) identified a small reduction in hippocampal volume in TEA cases they found no correlation between this atrophy and accelerated forgetting. It therefore might have been expected that RY’s memory would improve with successful medication. However his free recall performance after drug treatment is, in fact, little changed (and if anything his initial encoding of material is somewhat impaired). This suggests either that his ALF is not related to overt seizure frequency, or that the drug may have an amnestic effect which counteracts any benefits gained from reduced seizure frequency. Importantly for clinical practice, this suggests that even where medication eliminates overt seizures this will not necessarily resolve memory problems. This picture is slightly complicated by the fact that RY’s recognition memory performance improved following medication, going from below chance at the longest intervals to within normal limits. We can find no ready explanation for this pattern of results and since it is difficult to make a definitive statement from a single case study, this issue of possible improvement in recognition memory following anti-convulsant medication in cases of patients exhibiting accelerated forgetting warrants further study.

In addition, although RY has reported that his overt turns have ceased, this does not mean that all epileptiform activity has been eliminated. It is possible that subclinical seizures are still present, but are occurring within medial structures where they cannot be detected by standard scalp EEG. In an analysis of intracranial EEG reports Zangaladze et al. (2008) found that the majority of temporal lobe subclinical seizures originated from medial structures (amygdala or hippocampus) and remained localized within that region. A further possibility is that seizures are occurring during sleep. As reported in the Case History, the telemetry data used to diagnose TLE highlighted that RY experienced a greater number of partial seizures while asleep than while awake. No EEG monitoring during sleep has been performed since commencing treatment and it is therefore not possible to make an unequivocal statement on this issue. A possible link to sleep may be significant considering the mounting evidence for the importance of sleep to consolidation of declarative memories (e.g. Ellenbogen, Hulbert, Stickgold, Dinges & Thompson-Schill, 2006; Drosopoulos, Schulze, Fischer & Born, 2007). In addition, a clear association between waking and amnesic attacks in TEA has led Butler and Zeman (2008) to suggest the possibility that nocturnal subclinical epileptiform activity may be a causal factor in the memory deficits seen in this condition. EEG monitoring of inter-ictal brain activity over an extended period would be beneficial in clarifying the role of any remaining low-level epileptiform activity while awake or during sleep.

Although epilepsy remains a possible contributory factor in RY's ALF, it should be noted that explanations of ALF which limit themselves to the disruption of memory consolidation through temporal lobe epileptiform activity must explain why such functional impairments do not affect recall at short delays in ALF cases. Such

epileptiform activity might be expected to disrupt the function of the medial temporal lobes upon which this short term process is considered dependent (Mayes et al., 2003). Indeed, there are many cases of TLE patients who show just such impairments after short delays, (e.g. Giovagnoli & Avanzini, 1996), but yet a key characteristic of ALF is that memory function is normal for at least 30 minutes. One possible explanation is that the epileptiform activity in ALF cases may occur with low frequency, such that the amount encountered in a 30 minute period is insufficient to disrupt memory, while the amount encountered over 24 hours or several days is sufficient. Alternatively there may be low level disruption within 30 minutes which existing tests are insufficiently sensitive to detect. Indeed, in a preliminary study with RY, McGibbon, Jansari and Gaskell (2008) found evidence that ALF could be detected at a one hour delay within the 'clinical window', using a specially developed word-pair association test.

For non-repeatedly recalled information, RY's free recall was significantly impaired with respect to matched controls by the 24 hour test point. This reflects a relatively rapid onset of accelerated forgetting, and suggests the loss of information before secondary consolidation is complete, or disruption of the consolidation process itself. If such dysfunction(s) were the primary cause of ALF then memories that have been successfully consolidated would become immune to the effects of ALF. In this situation further regular recall or rehearsal may not be necessary to ensure memory retention. Such dysfunction could account for ALF cases where retrograde amnesia appears absent or has a steep temporal gradient (e.g. Kapur et al., 1997). However more extensive retrograde amnesia is present in many ALF cases (e.g. Ahern et al., 1994; De Renzi & Lucchelli, 1993; Lucchelli & Spinnler, 1998; Butler et al., 2007).

Such cases suggest either a further functional deficit, or perhaps a slowly developing ALF which has been operating for many years or even decades.

In contrast, a post-consolidation dysfunction would be expected to also affect strongly learned memories, suggesting that continual rehearsal may be necessary to maintain even successfully consolidated memories indefinitely, and that the immunity provided by repeated recall or rehearsal within the timeframe of this study may be temporary. Testing over extended time periods, controlling for level of rehearsal or recall, would be necessary to confirm this; to our knowledge no such testing has yet been published. Further work with RY to investigate the extent of any retrograde amnesia and the long term immunity effects of repeated recall would therefore be useful in distinguishing between causal deficits.

It should be noted, however, that ALF is not always accompanied by extensive retrograde amnesia (e.g. Kapur et al., 1997), and that therefore post-consolidation dysfunctions cannot be the sole cause of all ALF cases. A further possibility, therefore, is that both secondary consolidation and post-consolidation dysfunctions can cause ALF, either independently or in combination, and that patterns of impairment displayed in each case will depend on the combination of dysfunctions present.

It is interesting to compare RY's memory deficits with those reported in TEA cases. In addition to the recurrent transient attacks of amnesia that characterise TEA, most patients also experience persistent interictal memory difficulties. 44% of TEA patients report ALF, 70% report a patchy amnesia for remote autobiographical

events, and 36% report navigational difficulties (Butler et al., 2007). In addition to the ALF discussed in the current study, RY also displays retrograde amnesia for autobiographical events (not reported here), and reports navigational difficulties. However, he has never experienced the transient amnestic episodes which are one of the diagnostic criteria for TEA (Zeman, Boniface & Hodges, 1998). RY does not, therefore, meet the criteria for TEA. However, similarities in persistent memory deficits suggest possible commonalities in underlying pathology or causal mechanisms. Further study will be required to clarify any such relationship.

For repeatedly recalled material RY shows clear evidence of consolidation, with performance maintained at normal levels to 4 weeks for both recognition and free-recall. For these stories the same stimuli were repeatedly recalled (without re-presentation) at multiple intervals (and thus more frequently than in other ALF studies e.g. Blake et al., 2000; Mayes et al., 2003; Butler et al., 2007). Modern consolidation theories (e.g. Alvarez & Squire, 1994) suggest that memories are not passed to a long-term store in a single 'one-off' process (ALF patients serve as good evidence for this), but rather need to be consolidated after initial learning, a process which may include further reorganization and maintenance of memory traces each time a memory is recalled (Paller, 1997). Evidence for this is supported by studies measuring neural activity associated with the hippocampus and neocortex (e.g. Squire & Alvarez, 1995; Morrison, Allardyce & McKane, 2002). Such consolidation and memory reinforcement appears to have been facilitated for RY by the process of repeated recall and recognition testing at the assigned time intervals, providing him with relative immunity from abnormal forgetting, at least for the timeframe of this study.

In tests of free-recall for non-repeatedly recalled prose material, however, such reinforcement was not possible and here RY displayed a marked pattern of accelerated forgetting (reflecting patterns of other ALF patients e.g. Kapur et al., 1996; Mayes et al., 2003), reaching floor levels by two weeks. ALF cases such as RY and JL (Mayes et al., 2003), displaying strong evidence for some kind of initial 'rehearsal immunity', highlight the importance of further investigation into the immunity effects for strongly learned and frequently rehearsed information. In particular, ALF patients' accelerated forgetting of episodic memories, combined with their apparent responsiveness to repeated recall, highlights the benefits on long-term memory from repeated, spaced review of material. This technique has been found useful in improving autobiographical memory by repeated exposure to photographic images of earlier experiences that were generated by 'SenseCam', a portable, automatic camera (e.g. Berry et al., 2007). Such testing may also help distinguish between competing models of memory. If ALF cases show equal rehearsal-immunity for both semantic and episodic information then this would support models that postulate the relocation of both semantic and episodic memory indexing from the MTL to the neocortex (e.g. Alvarez & Squire, 1994). In contrast, if rehearsal-immunity differentially benefits semantic information then this would favour those models which maintain that while semantic indexing may relocate to the neocortex, episodic memory indexing remains reliant on the MTL indefinitely (Nadel & Moscovitch, 1997).

The current case study has contributed to the body of evidence for ALF through the presentation of a single-case study of a neurological patient, providing further

evidence of a class of patients who pass standard clinical tests of memory, yet display significant memory problems. Objective evidence for similar levels of accelerated forgetting both before, and after, medication has indicated that anticonvulsant drugs alone cannot account for ALF, and that such medication does not necessarily ameliorate ALF even where overt seizures cease. This case highlights the importance of pursuing further investigations into the immunity effects of various forms of rehearsal (active recall, passive representation, etc.) on memory for different types of material (verbal, visual, etc.) through detailed examinations of ALF patient memory profiles, and the possibility of using such techniques as the basis of protective strategies. Finally, the present study indicates the need for further exploration of any potential links between memory performance and (sub-clinical) epileptiform activity, especially during sleep. Further study of such patients should eventually lead to a better understanding of the underlying functional deficit(s) of ALF, and to advances in neurobiological and theoretical models of memory consolidation generally.

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