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Accelerated forgetting of real-life events in Transient Epileptic Amnesia

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Transient Epileptic Amnesia (TEA) is a form of temporal lobe epilepsy associated with ictal and interictal memory disturbance. Some patients with TEA exhibit Accelerated Long-term Forgetting (ALF), in which memory for verbal and non-verbal material is retained normally over short delays but fades at an unusually rapid rate over days to weeks. This study addresses three questions about ALF in TEA: i) whether real-life events undergo ALF in a similar fashion to laboratory-based stimuli; ii) whether ALF can be detected within 24 hours; iii) whether procedural memories are susceptible to ALF. Eleven patients with TEA and eleven matched healthy controls wore a novel, automatic camera, SenseCam, while visiting a local attraction. Memory for images of events was assessed on the same day and after delays of one day, one week, and three weeks. Forgetting of real-life events was compared with forgetting of a word list and with performance on a procedural memory task. On the day of their excursion, patients and controls recalled similar numbers of primary events, associated secondary details (contiguous events, thoughts and sensory information) and items from the word list. In contrast, patients showed ALF for primary events over three weeks, with ALF for contiguous events, thoughts and words over the first day. Retention on the procedural memory task was normal over three weeks. The results indicate that accelerated forgetting in TEA: i) affects memory for real-life events as well as laboratory stimuli; ii) is maximal over the first day; and iii) is specific to declarative memories.

Keywords: transient epileptic amnesia; memory; epilepsy; accelerated forgetting.

Word count: 6237 words

1. Introduction

Transient epileptic amnesia (TEA) is a form of temporal lobe epilepsy (TLE) in which recurrent episodes of transient amnesia are the principle manifestation of the seizure disorder (Kapur, 1990; Zeman, Boniface & Hodges, 1998; Butler et al., 2007). The condition typically arises in later life. Its cause is unknown. TEA can be distinguished from transient global amnesia (TGA) by the recurrence and brevity of its amnesic attacks, which typically last between 30 and 60 minutes. The amnesic attacks of TEA often occur upon waking and may be associated with other features of epilepsy, such as olfactory hallucinations. The amnesic episodes respond well to anticonvulsant medication in most cases. Nevertheless, many patients report unusual, persistent memory problems (Gallassi, 2006; Butler et al., 2009), including the 'evaporation' of memories for recent events within a few days or weeks. Their performance on standard memory tests is typically within the normal range (Zeman et al., 1998; Mendes, 2002). However, a recent study demonstrated accelerated forgetting of words and abstract designs over a period of three weeks (Butler et al., 2007).

This form of persistent memory impairment, in which excessively rapid forgetting occurs over days to weeks despite apparently normal learning and initial retention has been described since the early 1990s, in single cases and several case series, predominantly in the context of temporal lobe epilepsy (for reviews, see Bell & Giovagnoli, 2008; Butler & Zeman, 2008). The phenomenon, which has been termed accelerated long-term forgetting

(ALF, Butler et al., 2007), is clinically important since it corresponds to patients' subjective memory complaints (Butler et al., 2009) and yet is invisible to standard neuropsychological tests, which typically test memory retention over intervals of up to just 30 minutes. ALF is also of theoretical importance. In the psychological literature, it has generally been held that once information has successfully been encoded into long-term memory, forgetting occurs at a rate unaffected by neurological disease (Kopelman, 1985), interindividual differences (Maylor, 1993), gender (Mameniskiene, Jatuzis, Kaubrys & Budrys, 2006), or experimental manipulation (Slamecka & McElree, 1983; Underwood, 1954). The phenomenon of ALF challenges this assumption and may provide new insights into processes of long-term memory consolidation.

A number of important questions about ALF remain unanswered. Firstly, whilst ALF has been demonstrated using laboratory stimuli such as word-lists and meaningless visual designs (Butler et al., 2007; Manes, Graham, Zeman, de Lujan-Calcagno, & Hodges, 2005), it has not been systematically investigated using memories for real-life events. Complaints of poor everyday memory are common amongst patients with epilepsy (Vermeulen, Aldenkamp & Alpherts, 1992) and yet these subjective complaints often fail to correlate with objective performance on standard neuropsychological tests of memory (e.g. Corcoran & Thompson, 1992). These discrepancies may arise because subjective complaints are misleading: patients' awareness of their own memory problems may be inaccurate (Sunderland, Harris & Baddeley, 1983), mood disorders may give rise to spurious complaints of memory dysfunction (Corcoran & Thompson, 1992), or patients may use coping strategies in daily life that compensate for their cognitive deficits

(Dubreuil, Adam, Bier, & Gagnon, 2006). However, they may also reflect the limited 'ecological validity' of traditional neuropsychological tests, such as word-list recall, which may fail to identify problems with memory which matter in everyday life (Chaytor & Schmitter-Edgecombe, 2003). Understanding the relationship between standard memory tests and real-life memory problems is important in predicting everyday function. However, few studies have examined forgetting in epilepsy using ecologically valid stimuli.

Secondly, the time course of ALF is uncertain. The interval between learning and memory testing has varied across previous studies of ALF: the phenomenon has been reported over delays ranging from 24 hours (Martin et al., 1991) to eight weeks (Blake, Wroe, Breen, & McCarthy, 2000). Most studies have relied on a 30-minute standard delay, and a single longer delay to probe very-long term retention. However, in order to assess the shape of the forgetting curve, memory needs to be probed at several time delays after learning (e.g. Giovagnoli, Casazza & Avanzini, 1995; Butler et al., 2007). Using delays of 30 minutes, one week and three weeks, Butler et al. (2007) found the most pronounced forgetting in patients with TEA to occur between 30 minutes and one week. Given the association between the amnesic episodes of TEA and waking from sleep, Butler et al. (2007) suggested that nocturnal seizure activity in this condition might interfere with memory consolidation processes that are thought to depend upon sleep. If this is the case, it might be expected that ALF will be evident one day after learning.

Thirdly, it is not known whether ALF affects both declarative and non-declarative memories. Patients with amnesia due to lesions of the medial temporal lobes typically show impaired memory for events and facts (e.g. Scoville & Milner, 1957; Rosenbaum et al., 2008) but normal long-term retention of newly acquired skills (e.g. Corkin, 1968; Reber & Squire, 1998). Given the apparent association of ALF with epilepsy arising from temporal lobe foci, it may be that only declarative memories are affected. If, on the other hand, non-declarative memories such as learning and retention of new motor skills are also forgotten excessively rapidly, then the pathophysiological abnormalities underlying ALF may extend beyond the medial temporal lobes.

In this study, we therefore address the following three questions about ALF in a group of patients with TEA and matched, healthy control subjects: i) Can ALF be detected using stimuli derived from real-life events and, if so, how does this relate to performance on laboratory measures? ii) Over what time scale does accelerated forgetting occur? iii) Does ALF affect both declarative and procedural memory?

To obtain stimuli from real-life events, we used a novel wearable camera, SenseCam (Hodges et al., 2006), which is activated by a range of environmental sensors (Berry et al., 2007). The automatic capture of images confers additional ecological validity because it minimises intentional encoding of the items that will later be tested. Furthermore, as the images taken are contextually rich they can be used to assess both quantitative recall of events (which we term ‘primary events’) and also contextual details about that event (which we term ‘secondary details’), such as the temporal context, associated thoughts

and sensory information from that time. This allows a more fine-grained analysis of retained memories, of the kind used in studies of autobiographical memory (e.g. Levine et al., 2002; Milton et al., 2010). To ensure that the SenseCam images were sufficiently varied and reflected relatively unique events, participants wore a SenseCam during a visit to a local attraction. Forgetting was assessed at several intervals over a period of three weeks using images of the day's activities from the photographic diary. As SenseCam captures images approximately every 30 seconds this approach has the advantage that the large number of resulting images makes it possible to test memory at different intervals using different subsets of the images. In order to compare the SenseCam test with more conventional stimuli, participants' forgetting of a word-list was assessed over the same time period.

The Serial Reaction Time Task (SRTT, Nissen & Bullemer, 1987) was used to investigate procedural memory. In this well-established task, participants respond as quickly as possible to visual stimuli presented in one of four locations on a computer screen. Reaction times are compared across conditions in which stimuli are either presented in a repeating sequence of locations, or are presented in random locations. Healthy subjects show faster reactions over time and respond quicker to sequence trials than random trials (Nissen & Bullemer, 1987). Performance on the SRTT is normal in patients with amnesia caused by diencephalic or medial temporal lesions, although patients have no conscious recollection of having previously encountered the task (Nissen & Bullemer, 1987; Nissen, Willingham & Hartman, 1989; Reber & Squire, 1994). In contrast, impaired learning on the SRTT has been seen in patients with basal ganglia or

cerebellar damage (Pascual-Leone et al., 1993) and in healthy subjects following disruption of prefrontal or cerebellar function with transcranial magnetic stimulation (Robertson, Tormos, Maeda, & Pascual-Leone, 2001; Torriero, Olivieri, Koch, Catagirone, & Petrosini, 2004). The role of the basal ganglia in SRTT learning has also been demonstrated in studies using functional magnetic resonance imaging (fMRI) (Rauch et al., 1998). We assessed retention on the SRTT to determine whether ALF can be detected in forms of memory that do not rely upon the limbic system.

In sum, this study tested the following three hypotheses: i) Patients will show greater forgetting of primary events, secondary details, and word-lists than controls; ii) In line with Martin et al. (1991), patients will show significantly greater forgetting than controls over the first 24 hours after acquisition on the SenseCam and list-learning tests; iii) As procedural learning and retention have been found to be normal in patients with medial temporal lobe damage (Reber & Squire, 1998), retention on the SRT will not significantly differ between patients and controls.

2. Methods

2.1 Participants

Eleven patients (10 male, 1 female) meeting diagnostic criteria for TEA, and reporting symptoms suggestive of ALF, were recruited from around the United Kingdom via the TIME (The Impairment of Memory in Epilepsy) Project (Butler et al., 2007). The diagnostic criteria for TEA were: (1) a history of recurrent witnessed episodes of transient amnesia; (2) cognitive functions other than memory judged to be intact during typical

episodes by a reliable witness; (3) evidence for a diagnosis of epilepsy on the basis of one or more of the following: epileptiform abnormalities on electroencephalography (EEG), the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations), a clear-cut response to anticonvulsant therapy (Zeman et al., 1998). All patients complained spontaneously of losing memories over days or weeks more rapidly than they would expect. Ten patients had undergone MRI and one patient a CT scan of the brain. Only one probably causative abnormality (a petrous ridge meningioma) was detected. At the time of testing, all patients were on anticonvulsant monotherapy and had been seizure free for over four months. No seizures occurred during the three-week period of testing.

Each patient nominated a family member or friend as control subject. These 11 neurologically healthy adults (1 male, 10 female) were well matched to the patients with regard to age and IQ (see Table 1).

We explained to participants that the purpose of the study was to investigate aspects of learning and memory in patients with epilepsy. The operation of the SenseCam was outlined and participants were informed that memory for events during their outing would be tested later.

The study was approved by the Cornwall and Plymouth Research Ethics Committee (NHS-REC 07/H0203/271). All participants gave written, informed consent.

INSERT TABLE 1 ABOUT HERE

2.2 Neuropsychological test battery

A battery of standard neuropsychological tests was administered to patients and control subjects to assess current and premorbid levels of intelligence (the Wechsler Abbreviated Scale of Intelligence, Wechsler, 1999; and Wechsler Test of Adult Reading, Wechsler, 2001), anterograde memory (immediate and 30 minute delayed recall of a prose passage from the Wechsler Memory Scale-III; copy and 30 minute delayed recall of the Rey-Osterrieth Complex Figure, Osterrieth & Rey, 1944; word and face recognition on the Warrington Recognition Memory Test, Warrington, 1984), as well as levels of depression and anxiety (the Hospital Anxiety and Depression Scale, Zigmond & Snaith, 1983).

2.3.1. Real-life event memory procedure

The SenseCam (sized 6.5cm wide x 7cm high x 1.5cm long) is built around a PIC 18F8722 6 MIPS microcontroller with 128KB of flash memory (Hodges et al., 2006). The SenseCam (see Fig 1a) is worn around the neck and pictures are captured using a fish eye lens. This maximizes the field-of-view and ensures that objects at head height are photographed. Images are captured automatically approximately every 30 seconds.

INSERT FIGURE 1 ABOUT HERE

2.3.2. SenseCam image acquisition and selection

Each patient and their nominated control wore a SenseCam during a visit to a local attraction, chosen by the experimenter, to provide a novel and interesting environment for memory encoding. In nine cases, participants were taken to a castle or stately home and grounds; in one case a cooperage; and in one case a science museum (see Fig.2). Whilst it would have been ideal to use the same attraction for all participants, their geographical dispersion made this impossible. The case-control design was used to minimise any resulting bias. The patient and nominated control were asked to remain together for the majority of the excursion. The mean duration of the excursions was 3 hours 7 minutes (range: 2hours 40min – 3hours 50min).

Following the excursion, images from both patient and control SenseCams were downloaded and reviewed by the researcher and photographs of 20 isolated events were extracted. Events were activities that took place within a single clearly defined spatial context (e.g. the kitchen of a stately home or the rose garden), allowing the visit to be broken down into a linear set of events (one such event can be seen in Fig. 1b). For each event, five sequential images were chosen, except in cases in which two or more images were identical, in which case only one of these images was chosen. To minimise unsystematic variation between patient and control images (e.g. differences in lighting), patients and controls were both shown images of the events taken from the patient's SenseCam, except in cases where substantial differences in viewpoint occurred (e.g. patients and controls in different parts of the same room). This occurred in 21 events (9.5% of all events). In these cases, patients and controls viewed their own respective images of those same events.

INSERT FIGURE 2 ABOUT HERE

2.3.3. SenseCam event memory testing

Memory for events was tested at intervals of i) approximately three hours, ii) one day, iii) one week and iv) three weeks after SenseCam image acquisition. Five different events were selected for each test session. For each event, participants were shown five photographs (as described above). Photographs were presented on a Dell D830 laptop, and measured 125mm (width) by 90mm (height). Presentation times for each photograph were not fixed, and participants were allowed to view the photographs as many times as they wished. For each set of images, participants were initially asked to recall the event pictured (*primary event recall*: 1 point if correct, e.g. "We had just walked into the main hall"; 0 points if incorrect). Then, participants were asked to recall other secondary details associated with that event. This consisted of the events that immediately preceded and followed that event (*contiguous event recall*: 2 points if both correct; 1 point if only one correct; 0 points if neither correct); the participant's thoughts regarding that event (*thought recall*: 2 points if specifically about that point in time, e.g. "I remember seeing two girls playing with a tennis ball near there, which I thought was odd."; 1 point for a vague thought not specific to that moment in time, e.g. "I quite liked the museum"; 0 points if they failed to recall any thoughts), and sensory information (sounds, smells and temperature) regarding the event (*sensory information*: for each event, a mean score was derived by awarding one point for each of the three types of sensory information present and dividing by three). To ensure that associated detail measures (i.e. contiguous event

recall, thought recall and sensory information recall) were not affected by overall forgetting of events, this data was only analysed for correctly recalled events.

2.4. Word-list test

A list of 20 words, taken from the word-list learning and interference trials of the Adult Memory and Information Processing Battery (Coughlan & Hollows, 1985), was used to assess verbal memory. Words were presented orally over a minimum of five trials until the participant attained 80% accuracy (i.e. 16 words) at free recall, or until a maximum of 10 trials had occurred. After the learning trials, participants were administered a distractor task (odd/even judgement of numbers) for 40s to prevent rehearsal of the words, and limit the effects of working memory on initial recall. Recall of the words was then assessed immediately after the distractor task (40 seconds) and after 30 minutes, one day, one week, and three weeks. Subjects were not forewarned about the delayed probes, but were explicitly requested not to rehearse the material.

2.5. Serial Reaction Time Test

The SRTT was created and run using E-prime (Psychological Software Tools, 2002), which collected reaction times and response data. During the task, four dashes were presented in a line in the centre of the screen, denoting the four possible locations for a cue. The cue was a red asterisk, measuring 0.4cm in diameter and positioned 1cm above one of the lines. Responses were made using four corresponding buttons underneath. These were the keys C, V, B and N, and subjects used the first two fingers of each hand to respond. The stimulus remained on the screen until a response was made, and

297 participants were instructed to respond as quickly as possible. The appearance of cues
298 occurred either in a series of random locations, or as part of a 12-item sequence. The
299 position sequence used was 1-2-4-3-1-3-2-1-4-2-3-4 (taken from Reber & Squire, 1998).
300 Each block consisted of 10 intermixed cycles of random (R = 12 random positions) and
301 sequence (S) trials in the order R-S-S-R-S-S-R-S-S-R (modelled on the procedure of
302 Curran, 1997). Each test session consisted of four blocks. SRTT sessions occurred at the
303 same time intervals as the word-list test: i.e. an initial session followed by repeated
304 sessions at delays of 30 minutes, one day, one week and three weeks. The presence of the
305 sequence was not disclosed to participants until after the final session.
306
307 2.6. Overall test protocol
308 The first test session occurred on the same day as the excursion (three to four hours later).
309 Participants were given the SenseCam test; were trained and tested on the list learning
310 task, with recall assessed after 40 second (i.e. following distractor task) and 30 minute
311 delays; and performed the SRTT twice, with an inter-session interval of 30 minutes.
312 SenseCam, list-learning and SRTT probes were readministered after delays of one day
313 (approximately 22 hours after the excursion and 16 hours after the first testing session),
314 one week and three weeks. Each session lasted approximately two hours. A battery of
315 standard neuropsychological tests was administered over these subsequent sessions.
316
317 2.7. Statistical Analysis
318 The performance of patients and controls on standard neuropsychological tests was
319 compared using independent samples t-tests or the Mann-Whitney U test where

appropriate. Performance at the shortest delay on the SenseCam and list learning tests were compared using independent samples t-tests, to assess whether groups were matched at this time. Rate of forgetting across all the delays was then analysed using repeated-measures Analysis of Variance (ANOVA) with factors of delay and group. In cases where this delay by group interaction was significant, planned comparisons were used to assess delay by group interactions between consecutive pairs of delays, so that the critical time window at which ALF occurs could be determined. Effect sizes for the ANOVAs were determined using partial η^2, where .14 is a large effect (Stevens, 2002).

Performance on the SRTT was analysed using reaction times for correct responses. The first twelve trials for the first session were considered practice trials and excluded from the analysis. Trials in which reaction times were greater than two standard deviations (i.e. the top five percentile) from a participant's mean at each testing session were removed. Mean random RT and mean sequence RT were calculated from the median reaction time for each twelve-trial set of random and sequence trials within a block, respectively. These mean scores for random and sequence trials were analysed using a repeated-measures ANOVA with factors of group, trial type (random vs. sequence), and block (1-20). *Sequence learning* scores were then calculated for each block by subtracting the sequence RT from the random RT. This learning score factors out non-specific influences on reaction times to provide a measure of sequence learning (Nissen & Bullemer, 1987). These sequence learning scores were then used to calculate *Sequence retention* by subtracting the mean sequence learning score in the final block of the first session from

that of the first block of each of the later sessions (e.g. 30-minute block 1 minus first-session block 4). Sequence retention scores across the four intervals were compared using a repeated-measures ANOVA with factors of group (TEA vs. control) and retention interval (30 minute session minus first session vs. one day minus first session vs. one week minus first session vs. three week minus first session).

3. Results

The demographics of the patient and control groups and their performance on the standard neuropsychological test battery are shown in Table 1. Independent-samples t-tests confirmed that no significant differences existed between the groups on the standardised anterograde memory tests or on the HADS (for all tests, $p>.1$). Patients performed slightly better than controls on the Rey figure copy (Mann-Whitney test: $U=30$, $p<.05$).

3.1. SenseCam Test

The performance of the patient and control groups on the primary event recall, contiguous event recall, thought recall, and sensory information recall subsections of the SenseCam test is shown in Figure 3.

3.1.1. Primary Event Recall (Figure 3a)

Patient and control groups did not differ significantly in their ability to recall events from SenseCam images on the same day ($t(20)=-0.6$, $p>.5$, $r=.13$). There were significant main effects of delay ($F(3,60)= 7.0$, $p<.001$, $\eta^2_p=.26$) and group ($F(1,20)=18.5$, $p<.001$,

366 η^2_p=.48), with poorer performance in the patient group. There was a significant delay by
367 group interaction (F(3,60)=4.1, p<.05, η^2_p=.17), with patients forgetting more rapidly
368 over time than controls. Planned comparisons did not however reveal significant
369 differences in the forgetting rates of the two groups between consecutive pairs of delays
370 (for all p>.1).
371
372 *3.1.2. Contiguous Event Recall (Figure 3b)*
373 Knowledge for events immediately preceding and following the images, relative to the
374 number of events recalled, did not differ between the two groups when tested on the same
375 day (t(20)=0.2, p>.8, r=.04). Across the four delays there were significant main effects of
376 delay (F(3,60)=5.8, p<.01, η^2_p=.22) and group (F(1,20)=31.2, p<.001, η^2_p=.61), with
377 poorer performance overall by patients. There was also a significant delay by group
378 interaction (F(3,60)=10.7, p<.001, η^2_p=.34), with planned comparisons revealing
379 significantly greater forgetting in patients than controls between same day and one day
380 delays (F(1,20)=19.2, p<.001, η^2_p=.49), but not between one day and one week delays, or
381 between one week and three week delays (for both p>.7).
382
383 *3.1.3. Thought recall (Figure 3c)*
384 When tested on the same day, the two groups showed no difference in recall of thoughts
385 about the events, relative to the number of events recalled (t(20)<0.1, p>.9, r=.02).
386 Analysis of forgetting rates over the four delays revealed significant main effects of delay
387 (F(3,60)=9.5, p<.001, η^2_p=.32) and group (F(1,20)=12.0, p<.01, η^2_p=.38), with poorer
388 overall recall of thoughts in the patient group. There was also a significant delay by group

389 interaction ($F(3,60)=4.2$, $p<.01$, $\eta^2_p=.17$). Planned comparisons revealed significantly
390 greater forgetting of thoughts in patients than controls between same day and one day
391 delays ($F(1,20)=5.7$, $p<.05$, $\eta^2_p=.22$), but not between one day and one week, or between
392 one week and three week delays (for both $p>.1$).
393
394 INSERT FIGURE 3 ABOUT HERE
395
396 *3.1.4. Sensory information recall (Figure 3d)*
397 The two groups showed no difference in proportionate recall of sensory information
398 (sounds, smells, and temperature) recalled from the events when tested on the same day
399 ($t(20)=-1.4$, $p>.1$, $r=.29$). Analysis of forgetting rates over the four delays revealed a
400 significant main effect of delay ($F(3,60)=3.2$, $p<.05$, $\eta^2_p=.14$) and a non-significant trend
401 for an effect of group ($F(1,20)=3.7$, $p=.069$, $\eta^2_p=.16$). Furthermore there was a non-
402 significant trend for an interaction between delay and group ($F(3,60)=2.6$, $p=.059$,
403 $\eta^2_p=.12$).
404
405 3.1.5. Effect of exclusion of poor learners
406 Three of the eleven patients, but none of the controls, failed to reach criterion on the list
407 learning task (see below). Although learning of a word-list is unlikely to be directly
408 related to encoding autobiographical details, the findings were reanalysed after excluding
409 these 'poor learners' and their matched controls, to ensure a general learning deficit in
410 this subset of patients did not account for the results. This did not affect the delay by
411 group interactions for primary event recall ($F(3,42)=3.9$, $p<.05$, $\eta^2_p=.22$), contiguous

412 event recall ($F(3,42)=5.4$, $p<.01$, $\eta^2_p=.28$), or sensory information recall ($F(3,42)=0.7$,
413 $p>.5$, $\eta^2_p=.05$). However the delay by group interaction for thought recall was no longer
414 significant ($F(3,42)=2.4$, $p>.05$, $\eta^2_p=.15$).
415
416 3.2. List Learning Test
417 Performance in the list-learning tests (Figure 4) was analysed both including and
418 excluding the poor learners.
419
420 Excluding the poor learners, independent samples t-tests found no significant difference
421 in the number of learning trials needed to meet the learning criterion by patients
422 (mean=6.4, SD=1.2) or controls (mean=5.6, SD=0.8; $t(17)=1.6$, $p>.1$, $r=.36$), or in words
423 recalled after the 40 second delay (patients: mean=13.4, SD=2.7; controls: mean=15.0,
424 SD=2.6; $t(17)=-1.3$, $p>.2$, $r=.30$). Analysis of forgetting rates revealed significant main
425 effects of delay ($F(2.2, 36.7)=43.0$, $p<.001$, $\eta^2_p=.72$) and group ($F(1,17)=8.6$, $p<.01$,
426 $\eta^2_p=.34$) with poorer recall across the five testing points in patients. There was also a
427 significant interaction between delay and group ($F(2.2, 36.7)=10.4$, $p<.001$, $\eta^2_p=.38$) with
428 planned comparisons revealing greater forgetting in patients between 30-minute and one
429 day delays ($F(1,17)=5.6$, $p<.05$, $\eta^2_p=.25$) and a non-significant trend for greater forgetting
430 between one day and one week delays ($F(1,17)=4.3$, $p=.054$, $\eta^2_p=.20$). In contrast,
431 forgetting rates did not differ between 40-seconds and 30-minutes ($p>.8$, $\eta^2_p<.01$), or
432 between one week and three week delays ($p>.1$, $\eta^2_p=.14$). Reanalysis of the data with
433 inclusion of the poor learners resulted in significantly poorer recall by patients at the 40
434 seconds delay ($t(20)=-2.3$, $p<.05$, $r=.46$) but had little effect on the pattern of interaction

results except that the group by delay interaction became significant between the one week and three week delays ($F(1,20)=4.7$, $p<.05$, $\eta^2_p=.19$), with greater forgetting in patients.

We investigated whether forgetting on the word-list between the 40 second and 30 minute delays correlated with forgetting between 30 minutes and one day (i.e. the period over which forgetting was most marked). Retention over these two intervals was correlated in controls ($r(11)=.7$, $p<.05$), but not in patients either including ($r(11)=-.2$, $p>.5$) or excluding ($r(8)=-.2$, $p>.5$) the poor learners. Thus, in controls, early forgetting predicts subsequent forgetting, but the same is not true for patients with ALF.

We investigated whether long-term forgetting rates on the word-list and the 'ecological' SenseCam task were correlated in all patients. We used percentage retention between initial recall (i.e. 40 seconds for list learning or same day for SenseCam tests) and both one day and three week probes (i.e. the periods over which forgetting was maximal), comparing word-list recall with recall of primary events, contiguous events, thoughts and sensory information. To account for the increased likelihood of a type I error for these eight analyses, results are reported at a Bonferroni-corrected significance level of $p=.006$ (i.e. $p=.05/ 8$). There were no significant correlations between one day retention of the word-list in patients and one day retention on primary event recall ($r(11)=-.01$, $p>.9$; Fig. 6a), contiguous event recall ($r(11)=.23$, $p>.4$; Fig. 6b), thought recall ($r(11)=-.27$, $p>.4$; Fig. 6c) or sensory recall ($r(11)=-.57$, $p>.05$; Fig 6d). Three-week retention of the word-list in patients was significantly correlated with three week retention on contiguous event

458 recall (r(11)=.81, p=.003; Fig. 6b) but not primary event recall (r(11)=-.37, p>.03; Fig.
459 6a), thought recall (r(11)=.09, p>.7; Fig. 6c), or sensory information recall (r(11)=-.51,
460 p>.1; Fig. 6d).
461
462 INSERT FIGURES 4 ABOUT HERE
463
464 3.3. Serial Reaction Time Task
465 Two patients and their respective controls did not take part in the SRTT task, due to the
466 effects of arthritis. Across all five sessions, patients made errors on a mean of 3.0% of
467 trials, whereas the controls made errors on a mean of 1.9% of trials. A repeated-measures
468 ANOVA carried out on the errors of the two groups across the five test sessions found no
469 effect of test session ($F(4,64)=1.3$, $p>.2$, $\eta^2_p=.08$), group ($F(1,16)=2.3$, $p>.1$, $\eta^2_p=.13$) or
470 any interaction between test session and group ($F(4,64)=0.9$, $p>.4$, $\eta^2_p=.05$).
471
472 3.3.2. *Procedural Learning*
473 Procedural learning was compared between patients and controls. The ANOVA revealed
474 a significant effect of trial type ($F(1,16)=37.4$, $p<.001$, $\eta^2_p=.70$) with faster responses to
475 sequence trials than random trials (see Fig 5a.). There was also a significant effect of
476 block ($F(19, 304)=22.1$, $p<.001$, $\eta^2_p=.58$) demonstrating learning on the task. There was
477 however no effect of group ($F(1,16)=0.9$, $p>.3$, $\eta^2_p=.06$) and no significant interactions
478 between trial type and group ($F(1,16)=0.1$, $p>.7$, $\eta^2_p<.01$), between block and group
479 ($F(19, 304)=0.9$, $p>.5$, $\eta^2_p=.06$) or between trial type, block and group ($F(19, 304)=0.9$,

480 $p>.4$, $\eta^2_p=.06$). This indicates that the groups did not differ in their rate of learning on the
481 SRTT, or on differential rates of learning on random and sequence trials.
482
483 3.3.3. *Sequence Retention*
484 Repeated-measures ANOVA was then carried out on sequence retention scores between
485 the first session and each of the later sessions. There was no effect of retention interval
486 ($F(3,48)=1.2$, $p>.3$, $\eta^2_p=.07$), group ($F(1,16)<0.1$, $p>.9$, $\eta^2_p<.01$) and no interaction
487 between retention interval and group ($F(3,48)=0.7$, $p>.5$, $\eta^2_p=.04$). This indicates that
488 memory for the sequence was similarly retained by both patient and control groups (see
489 Fig 5b.).
490
491 INSERT FIGURE 5 ABOUT HERE

492 ## 4. Discussion

493 We have explored the long-term retention of memory for real-life events, word-list and
494 procedural skills in patients with TEA and healthy controls. Patients showed accelerated
495 long-term forgetting (ALF) of everyday events over a three week period. They also
496 exhibited accelerated forgetting of contiguous events, thoughts and a word-list over the
497 first day after learning. Patients did not differ from controls in their learning or retention
498 of a newly acquired procedural motor skill.
499 We discuss our findings in relation to the three principle questions identified in
500 the introduction.
501

i) Can ALF be detected using stimuli from real-life events and, if so, how does this relate to performance on laboratory measures?

We have shown that ALF of real life events can be detected over one day – three weeks following learning in patients with TEA. ALF was apparent for memory of primary events with a large effect size over the entire three week period of observation. ALF of primary events is striking, given the informative nature of the probes. Indeed on this task, controls performed at or near ceiling at same day, one day and three week delays. ALF was equally marked for memory of contiguous events and associated thoughts with large effects over the first day following learning. There was a trend towards accelerated forgetting for memory of sensory information in patients which did not reach significance. This may be a relatively insensitive measure as it is easier to deduce information about sensory details from the visual cues than it is to remember contiguous events or concurrent events. Overall, therefore, there is both a quantitative loss and qualitative deterioration of everyday memories in TEA. The latter indicates that, over time, events that are recalled in TEA become stripped of the associative information that characterises episodic memory (see Tulving, 1972). Whether this reflects impaired consolidation, in which case the memories are lost, or reduced accessibility over time, in which case participants may recognise events given sufficient cueing, is unclear. The detection of ALF in patients with TLE on tests both of recall and recognition (Blake et al., 2000) suggests that the deficits may be due to impaired consolidation; this can be addressed in future studies by also employing tests of recognition. However, regardless of the mechanisms underlying forgetting, these results are in accordance with patients'

524 subjective reports of the ‘evaporation’ of memory for recent events (Butler & Zeman
525 2008).
526
527 One previous study has compared performance on lab-based tests to objectively measured
528 memory for real-life events over similar time frames in epilepsy. Helmstaedter, Hauff and
529 Elger (1998) found that recall of lists of words and designs after a one week delay
530 predicted one-week delayed recall of aspects of the testing session itself in TLE.
531 However, Helmstaedter et al. did not examine whether participants could recall aspects of
532 the testing session soon after learning and therefore did not assess the relationship
533 between forgetting on the two tasks. In the present study, patients were unimpaired on
534 recall of primary events and secondary details when tested on the same day, but impaired
535 at intervals of more than one day.
536
537 On word-list recall, where ceiling effects were avoided altogether, patients also exhibited
538 ALF. There was a strong correlation ($r = .8$) between forgetting of the word list over
539 three weeks and forgetting of contiguous events in the SenseCam study. At one day this
540 correlation was weaker ($r = .2$). This suggests that list-learning tests provide a valid
541 method for assessing some aspects of long-term forgetting in epilepsy but that forgetting
542 rates on these tests may only partially overlap, with similarities becoming more apparent
543 over longer delays. Forgetting of the word-list did not correlate with forgetting of primary
544 events or associated thoughts, despite the similar gradients of the forgetting curves (see
545 Figures 2 a and c, Figure 4). The weak correlation with memory for primary events may
546 reflect the relative insensitivity of this measure. The weak correlation between memory

for the word list and for associated thoughts may indicate differential rates of forgetting for different types of material – in this case memory for internal states (e.g. thought recall) as against memory for stimuli experienced as external (e.g. a word list).

It would be of great interest to know whether the ALF for real-life events documented in this study among patients with TEA can also be demonstrated in patients with other varieties of epilepsy. There is no reason to think that ALF is unique to TEA: it has clearly been described both in single cases (e.g. Kapur et al., 1997; Holdstock, Mayes, Isaac, Gong & Roberts, 2002; Mayes et al., 2003) and in group studies involving patients with other varieties of focal epilepsy (e.g. Martin et al., 1991; Blake et al., 2000; Mameniskiene et al., 2006; for a review, see Butler & Zeman, 2008), usually arising from the temporal lobes. Furthermore, the patients' impaired recall of secondary details seen in this study bears a resemblance to the impairment of autobiographical recall over longer time scales, in both patients with TEA (Milton et al., 2010), and patients with mesial temporal lobe amnesia (e.g. Rosenbaum et al., 2008). We suspect – though at present can not prove – that ALF is simply more common among patients with TEA than among patients with most other forms of focal epilepsy, because it directly involves key structures involved in memory processing. This is inline with our recent finding, of significant hippocampal atrophy in patients with TEA (Butler et al., 2009). Further work comparing long-term memory for real-life events in other varieties of epilepsy, and indeed in other neurological disorders, would therefore be worthwhile.

ii) What is the time scale of accelerated long-term forgetting?

We have found that ALF for both real-life events and for a word list is most pronounced over the first day of retention. Three other studies have assessed forgetting over a 24-hour interval in patients with TLE (Martin et al., 1991; Giovagnoli et al., 1995; Bell, Fine, Dow, Seidenberg & Hermann, 2005). Martin et al. (1991) matched patients and controls for initial learning and found impaired retention in patients over 24 hours. Giovagnoli et al. (1995) also matched patients and controls for initial learning but found no difference in retention after one day, three day, six day or thirteen day delays. However, at the thirteen day delay patients and controls still recalled approximately 90% of the stimuli, suggesting that ceiling effects may have influenced the results. In contrast, Bell et al. (2005) did not match groups for learning and subsequently found no difference in forgetting over the first 24 hours. Loftus (1985) has noted that differences in initial learning ability may confound analyses of forgetting rates. Specifically, when groups are mismatched for initial learning, forgetting rates can be underestimated in the lower-performing group as they have less to forget. It is therefore unclear whether patients in the Bell et al. study did indeed show normal forgetting. In the present study, we avoided ceiling effects by using an 80% learning criterion. Although three patients failed to meet our learning criterion, scaling problems cannot account for the present results. The inclusion of these patients would, if anything, have led to an underestimation of forgetting in patients. Furthermore, omission of these poor learners did not affect the findings for recall of events, contiguous events or word-lists. The occurrence of ALF over the first day of retention suggests that an interval of one or a few days should generally be sufficient for the detection of ALF in TEA.

593 The rate of forgetting in ALF may offer clues to the underlying pathophysiology. While a
594 subtle impairment of memory encoding remains a possible explanation for ALF, its
595 emergence at one day among patients with TEA who perform normally on memory tests
596 at 30 minutes, taken together with the dissociation between retention at 30 minutes and
597 one day, suggest impairment of an extended but relatively early process of memory
598 consolidation or, alternatively, loss of access to memories. Several mechanisms have
599 been posited for ALF, in particular anti-epileptic drugs (AEDs), clinical and subclinical
600 seizure activity, and structural brain pathology (Butler, Muhlert & Zeman, 2010). AEDs
601 are unlikely to have contributed substantially to ALF, given that ALF has been reported
602 both before and after administration of AEDs (Jansari et al., 2010), and that patients with
603 TEA, who often complained of ALF prior to anticonvulsant treatment, generally
604 responded well to only modest doses of anticonvulsants (Butler et al., 2007). Clinically
605 apparent seizures are not a necessary condition for ALF as patients in the present study
606 were seizure-free, but may well play a part in some patients (see Mameniskiene et al.,
607 2006). Subclinical seizure activity may also play a role, and forgetting is reported to be
608 accelerated in patients with TLE who show interictal EEG abnormalities (Mameniskiene
609 et al., 2006). Subclinical seizure activity during sleep could be particularly relevant in
610 patients with TEA, as sleep is thought to play a crucial role in the consolidation of newly
611 acquired memories (e.g. Marshall & Born, 2007), the amnesic attacks of TEA often occur
612 upon awakening (Butler et al., 2007) and ALF appears to be maximal over the first 24
613 hours following learning. Further work is therefore needed to explore the relationships
614 between sleep, interical epileptic discharges and ALF. Alternatively the structural

615 pathology underlying TEA may disrupt processes of memory storage and consolidation,
616 or accessibility, occurring over the hours and days following acquisition.
617
618 iii) Does ALF affect both declarative and procedural memory?
619 In the serial reaction time task, patients and controls showed normal procedural learning.
620 Sequence learning was then retained normally by patients with TEA. This supports our
621 prediction that procedural memory is intact in TEA. We did not directly investigate
622 whether participants became aware of the repeated sequence in 'sequence trials' but
623 previous work indicates that this is unlikely given the parameters used in our study
624 (Pascual-Leone et al., 1993; Curran, 1997).
625
626 The present findings are similar to those reported in patients with temporal lobe and
627 diencephalic amnesias, who also show intact sequence learning (Nissen & Bullemer,
628 1987; Reber & Squire, 1994; Reber & Squire, 1998), and intact retention of sequence
629 learning over one week delays (Nissen et al., 1989). In contrast, patients with basal
630 ganglia and cerebellar damage show impaired sequence learning on the SRTT (Pascual-
631 Leone et al., 1993; Vakil, Kahan, Huberman, & Osimani, 2000). This suggests that the
632 pathophysiology underlying ALF spares the basal ganglia and cerebellum and affects
633 structures involved in declarative memory such as the medial temporal lobe or
634 diencephalic region.
635
636 We acknowledge two particular limitations of the present study: first, the difference in
637 gender distribution between patients and controls, and, second, the small sample size. The

first limitation reflects the fact that patients typically nominated their partners as controls, As ten of the patients were male (reflecting the greater prevalence of TEA in males; Butler et al., 2007) the sex ratios of the patient and control groups differed. This is unlikely to account for our findings, given evidence that ALF is unrelated to gender (Mameniskiene et al., 2007). Second, although the effect sizes for ALF were medium to large, future work would undoubtedly benefit from use of larger, gender-matched groups.

In conclusion, this study provides the first direct evidence that ALF in patients with epilepsy affects retention of memory for real-life events. Among patients with TEA, recalled memories of significant events became less detailed over time, with loss of the associated information that characterises episodic memory. Retention of a word list at 30 minutes was correlated with retention at one day in controls but not in patients, in keeping with the suggestion that ALF reflects disruption of an extended but relatively early process of memory consolidation. As forgetting was maximal over the first day, future work should assess whether abnormalities of processes occurring during this time, such as impairment of consolidation during sleep, account for ALF of declarative memories in epilepsy. Word-list retention and recall of contiguous events correlated at three weeks in patients, indicating that word list recall at an extended delay can provide a useful index of memory for everyday events.

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814

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819 Table 1. Demographic and Neuropsychological profile of Transient Epileptic Amnesia
820 and Control groups.

	TEA Group (n=11) *Mean (SD)*	*Control Group (n=11)* *Mean (SD)*
Age, yr	68.6 (9.9)	66.0 (8.3)
Males: Females	10: 1	1: 10
IQ Measures		
WASI Full Scale IQ	122.7 (6.0)	119.6 (13.0)‡
WASI Verbal IQ	119.0 (7.5)	117.2 (10.3)
WASI Performance IQ	121.5 (9.8)‡	115.0 (17.4)†
WTAR Predicted Pre-morbid IQ	112.7 (5.9)	113.8 (5.5) †
Episodic memory scores (max score)		
Story recall immediate (25)	13.7 (3.8)	15.8 (4.5)
Story recall delayed (25)	11.6 (4.1)	14.6 (4.3)
Rey Complex Figure Delayed Recall (36)	16.8 (7.1)	18.1 (7.0)
Warrington Word Recognition (50)	47.2 (3.1)‡	47.8 (1.7) †
Warrington Face Recognition (50)	40.1 (4.4)‡	43.8 (2.5)†
Visuospatial perception (max score)		
Rey Complex Figure Copy (36)	35.9 (0.3)	34.6 (1.7)*
HAD Scores (max score)		
Anxiety Score (21)	7.5 (4.5)	5.1 (2.5)
Depression Score (21)	2.6 (1.4)	2.7 (2.3)

821 *: Mann-Whitney test revealed a significant difference between groups (U=30, $p<.05$). On all other tests,
822 independent samples t-tests found no significant differences between groups (for each, $p>.05$).
823 †: performance based on 9 participants.
824 ‡: performance based on 10 participants.
825

Figure Captions

Figure 1: a) a picture of SenseCam; b) the procedure for presenting SenseCam images.

Figure 2: Map showing type and location of events.

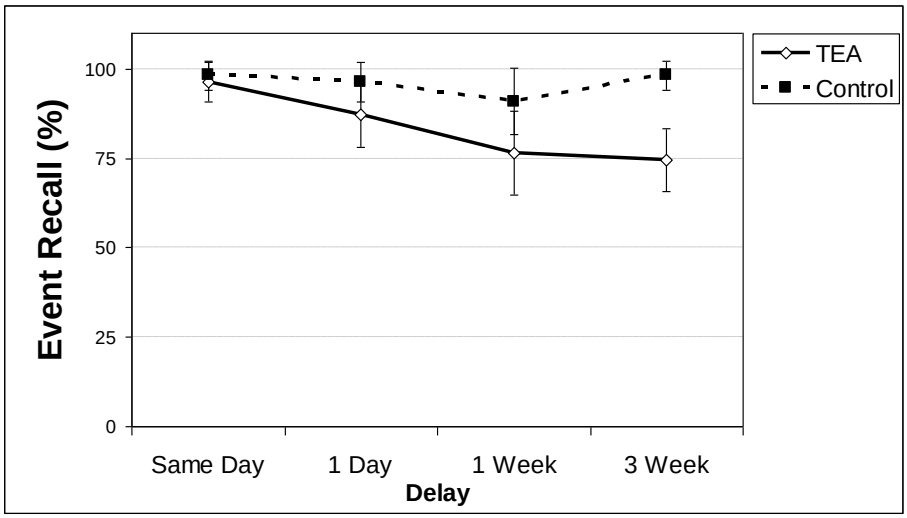
Figure 3: Mean performance on SenseCam measures when tested on the same day, and after delays of one day, one week and three weeks. a) recall of event shown in image b) recall of contiguous events (immediately preceding and following event shown), relative to events recalled; c) recall of thoughts from event, relative to events recalled. d) recall of sensory information, relative to events recalled. Error bars show 95% confidence intervals.

Figure 4: Mean recall performance of TEA and control groups on the list learning test at the last trial and after delays of 40 seconds, 30 minutes, one day, one week and three weeks. TEA = All patients with TEA; GL = TEA patients who were good learners (only those meeting the learning criterion). Error bars show 95% confidence intervals.

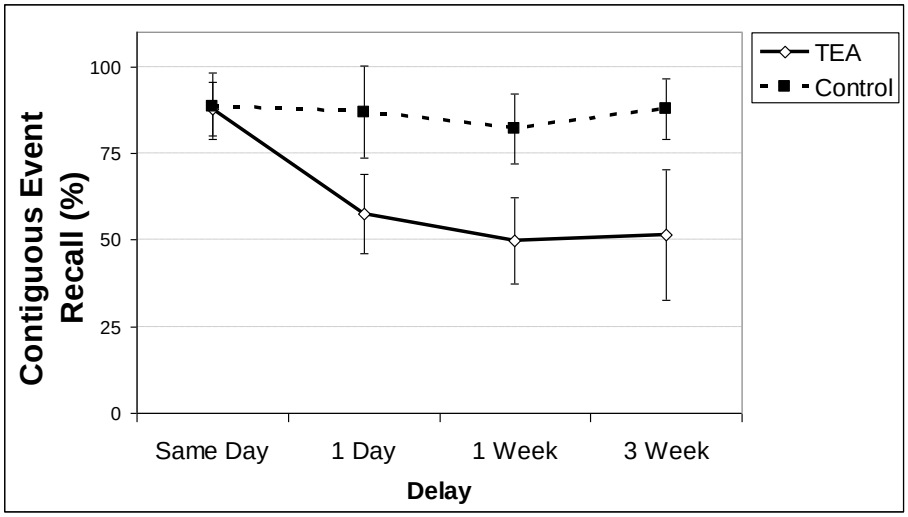
Figure 5: Performance on the serial reaction time task. a) Reaction times for both groups on sequence and random trials across all 20 blocks; b) Sequence Retention, as measured by change in random-sequence reaction times between first session and each of the subsequent delays. Error bars show 95% confidence intervals.

Figure 6: Correlations between retention on the list learning and SenseCam tests between 40 second or same day respectively, and one day (white triangles and dashed trend-line), or three weeks (red squares and unbroken trend-line) for patients with TEA. Figures show retention of a) primary events; b) contiguous events; c) thoughts; and d) sensory information. x2 = two overlapping data points.

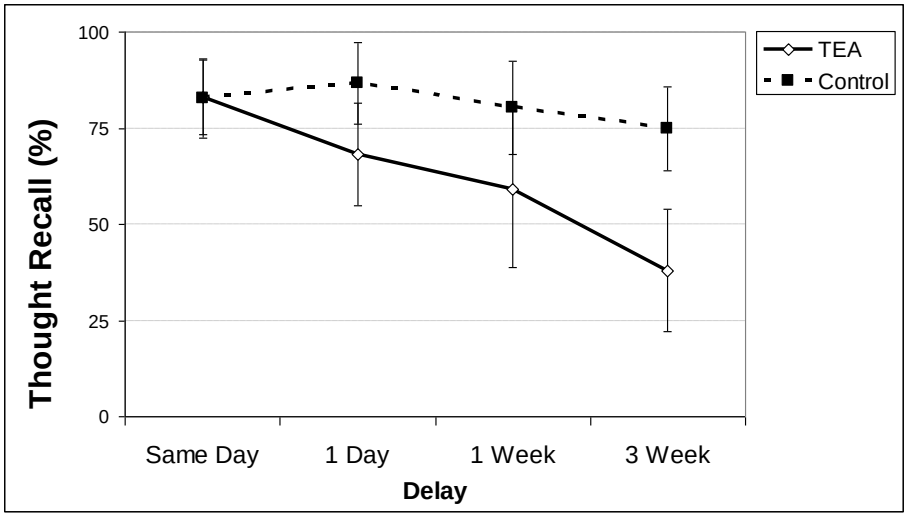
a.

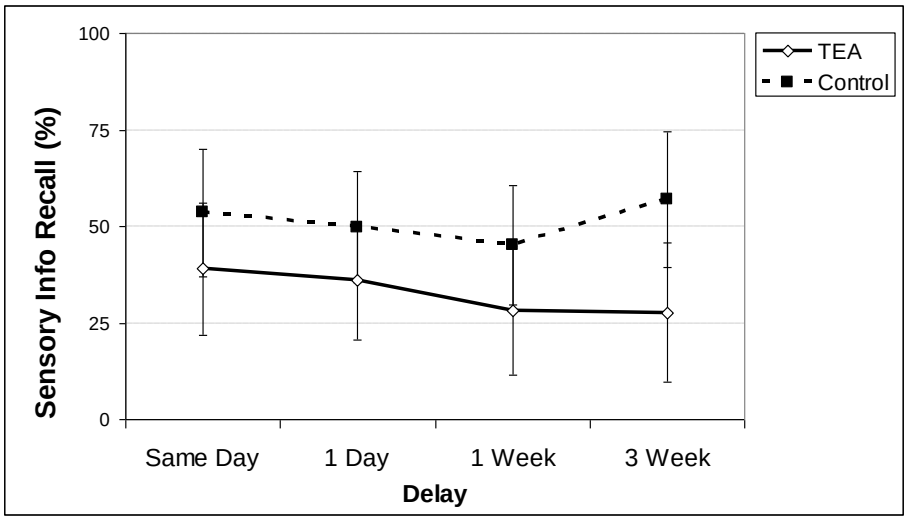

Event Recall (%)
100
75
50
25
0
Same Day
1 Day
1 Week
3 Week
Delay
TEA
Control

b.


Contiguous Event Recall (%)
100
75
50
25
0
Same Day
1 Day
1 Week
3 Week
Delay
TEA
Control

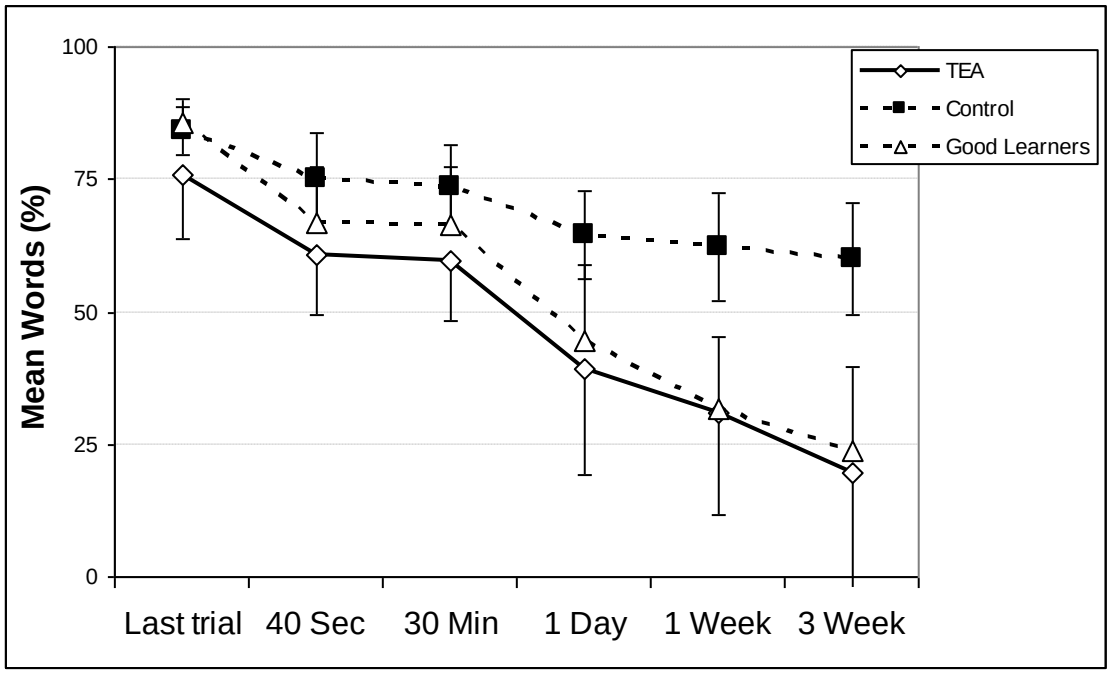
c.


Thought Recall (%)
100
75
50
25
0
Same Day
1 Day
1 Week
3 Week
Delay
TEA
Control


100
75
50
25
0
Sensory Info Recall (%)
Same Day
1 Day
1 Week
3 Week
Delay
TEA
Control

d.

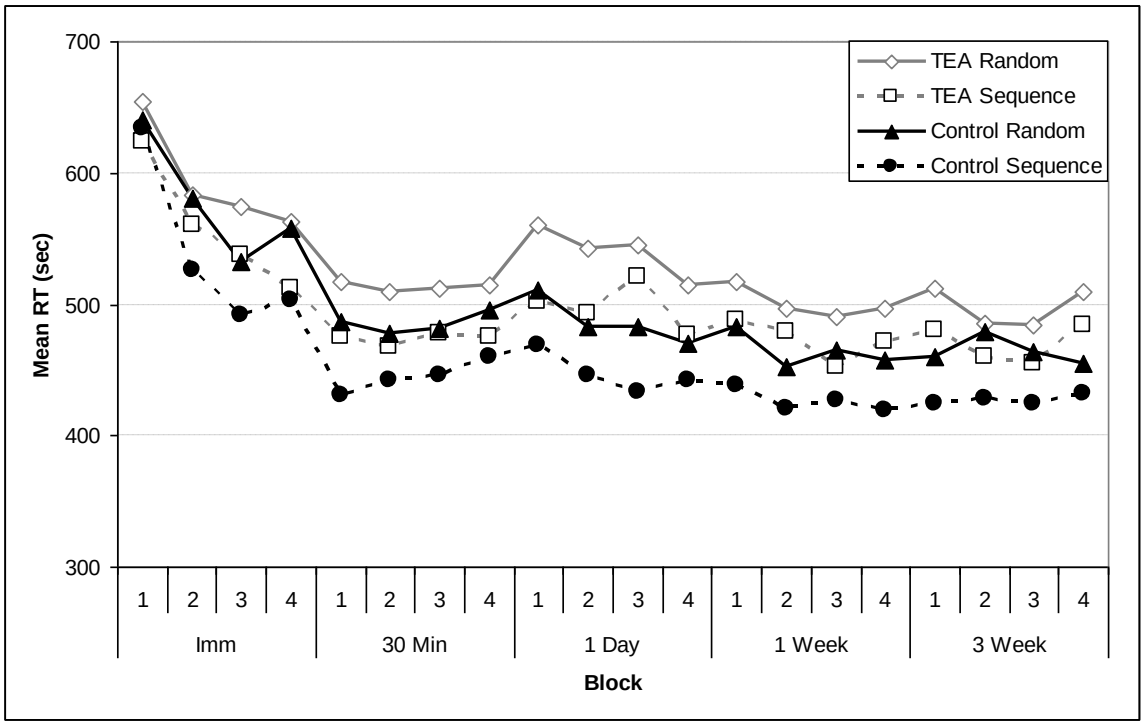
Figure 3.



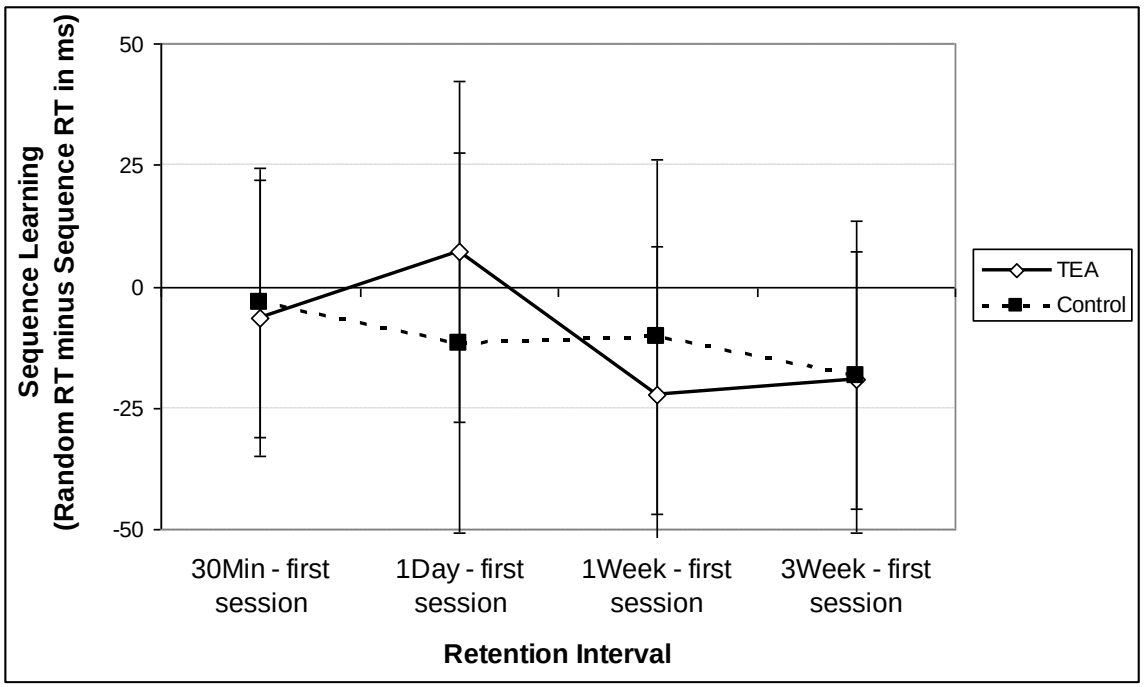
861

862 Figure 4.

863



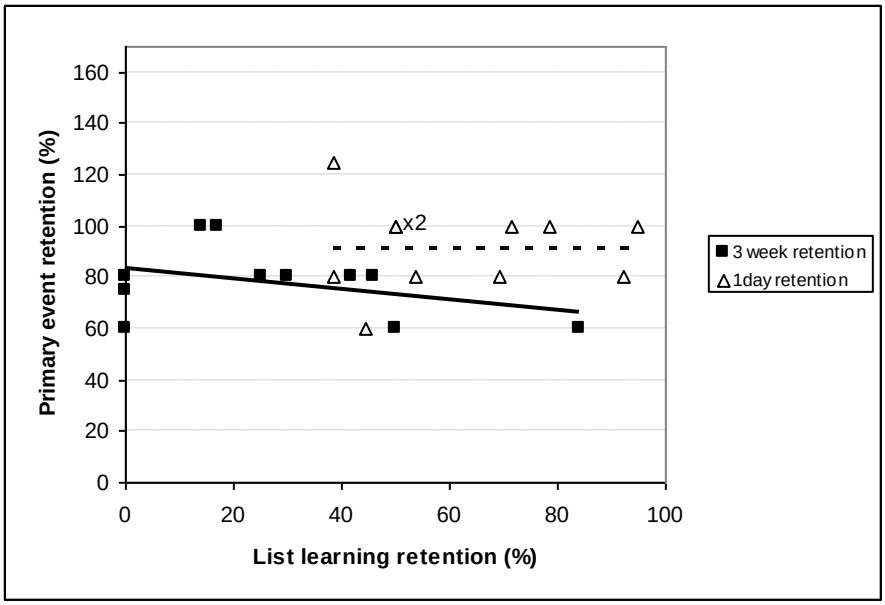
864 a.



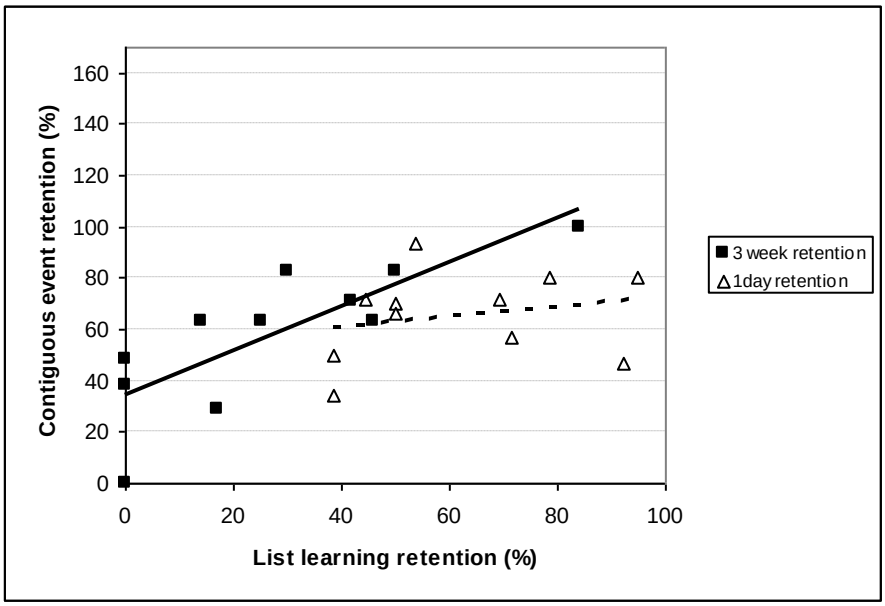
865 b.

866 Figure 5.

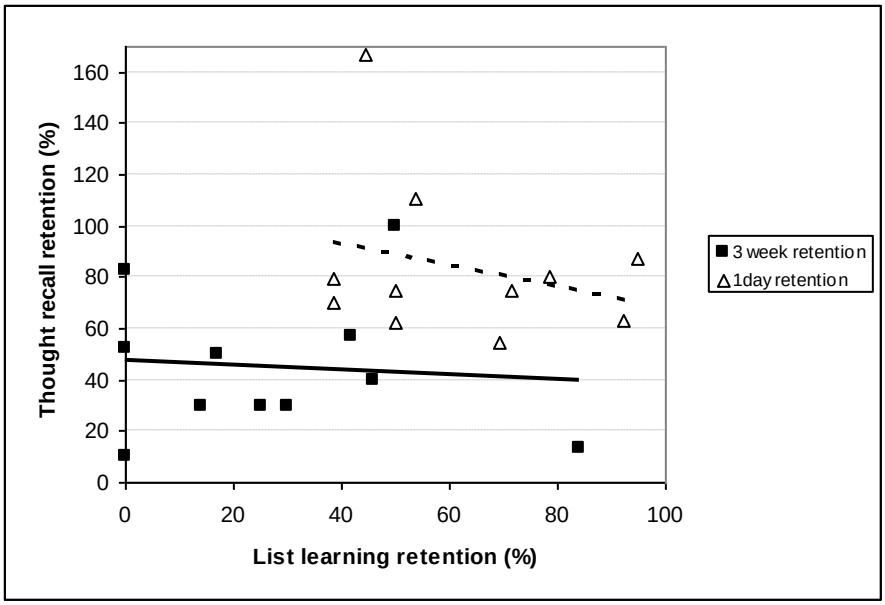
867


Primary event retention (%)
List learning retention (%)
x2
3 week retention
1day retention

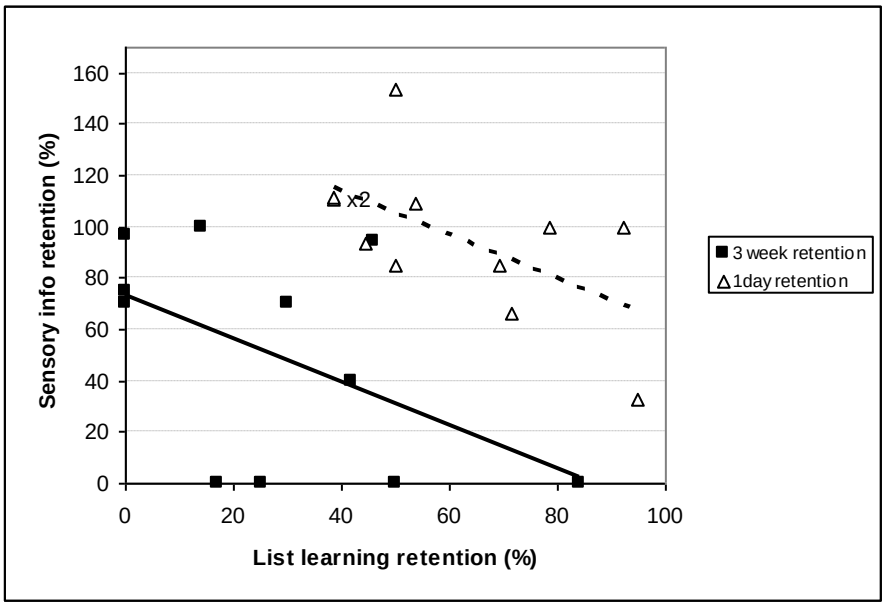
a.


Contiguous event retention (%)
List learning retention (%)
3 week retention
1day retention

b.


Thought recall retention (%)
List learning retention (%)
3 week retention
1day retention
0
20
40
60
80
100
120
140
160

c.


Sensory info retention (%)
List learning retention (%)
3 week retention
1day retention
0
20
40
60
80
100
120
140
160

d.

Figure 6.