

Accelerated forgetting of real-life events in Transient Epileptic Amnesia

Muhler, N.¹, Milton, F.², Butler, C.R.³, Kapur, N.⁴, & Zeman, A.Z.¹

1. Cognitive and Behavioural Neurology, Peninsula Medical School, Exeter, UK.

2. Department of Psychology, University of Exeter, Exeter, UK.

3. Department of Clinical Neurosciences, University of Oxford, Oxford, UK.

4. Neuropsychology Department, Addenbrooke's Hospital, Cambridge, UK.

Address for correspondence

Professor Adam Zeman

Cognitive & Behavioural Neurology

PMS Building

Exeter

UK

EX2 5DW

Tel: +44 1392 406 754

E-mail: adam.zeman@pms.ac.uk

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

42

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

44 **Word count:** 6237 words

45

46

47 **1. Introduction**

48

49 Transient epileptic amnesia (TEA) is a form of temporal lobe epilepsy (TLE) in which
50 recurrent episodes of transient amnesia are the principle manifestation of the seizure
51 disorder (Kapur, 1990; Zeman, Boniface & Hodges, 1998; Butler et al., 2007). The
52 condition typically arises in later life. Its cause is unknown. TEA can be distinguished
53 from transient global amnesia (TGA) by the recurrence and brevity of its amnesic attacks,
54 which typically last between 30 and 60 minutes. The amnesic attacks of TEA often occur
55 upon waking and may be associated with other features of epilepsy, such as olfactory
56 hallucinations. The amnesic episodes respond well to anticonvulsant medication in most
57 cases. Nevertheless, many patients report unusual, persistent memory problems (Gallassi,
58 2006; Butler et al., 2009), including the ‘evaporation’ of memories for recent events
59 within a few days or weeks. Their performance on standard memory tests is typically
60 within the normal range (Zeman et al., 1998; Mendes, 2002). However, a recent study
61 demonstrated accelerated forgetting of words and abstract designs over a period of three
62 weeks (Butler et al., 2007).

63

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

69 (ALF, Butler et al., 2007), is clinically important since it corresponds to patients'
70 subjective memory complaints (Butler et al., 2009) and yet is invisible to standard
71 neuropsychological tests, which typically test memory retention over intervals of up to
72 just 30 minutes. ALF is also of theoretical importance. In the psychological literature, it
73 has generally been held that once information has successfully been encoded into long-
74 term memory, forgetting occurs at a rate unaffected by neurological disease (Kopelman,
75 1985), interindividual differences (Maylor, 1993), gender (Mameniskiene, Jatuzis,
76 Kaubrys & Budrys, 2006), or experimental manipulation (Slamecka & McElree, 1983;
77 Underwood, 1954). The phenomenon of ALF challenges this assumption and may
78 provide new insights into processes of long-term memory consolidation.

79

80 A number of important questions about ALF remain unanswered. Firstly, whilst ALF has
81 been demonstrated using laboratory stimuli such as word-lists and meaningless visual
82 designs (Butler et al., 2007; Manes, Graham, Zeman, de Lujan-Calcano, & Hodges,
83 2005), it has not been systematically investigated using memories for real-life events.
84 Complaints of poor everyday memory are common amongst patients with epilepsy
85 (Vermeulen, Aldenkamp & Alpherts, 1992) and yet these subjective complaints often fail
86 to correlate with objective performance on standard neuropsychological tests of memory
87 (e.g. Corcoran & Thompson, 1992). These discrepancies may arise because subjective
88 complaints are misleading: patients' awareness of their own memory problems may be
89 inaccurate (Sunderland, Harris & Baddeley, 1983), mood disorders may give rise to
90 spurious complaints of memory dysfunction (Corcoran & Thompson, 1992), or patients
91 may use coping strategies in daily life that compensate for their cognitive deficits

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

99

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

113

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

123

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

129

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

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

148

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

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

167

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

175

176 **2. Methods**

177 2.1 Participants

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

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

193

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

197

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

202

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

205

206 INSERT TABLE 1 ABOUT HERE

207

208 2.2 Neuropsychological test battery

209 A battery of standard neuropsychological tests was administered to patients and control
210 subjects to assess current and premorbid levels of intelligence (the Wechsler Abbreviated
211 Scale of Intelligence, Wechsler, 1999; and Wechsler Test of Adult Reading, Wechsler,
212 2001), anterograde memory (immediate and 30 minute delayed recall of a prose passage
213 from the Wechsler Memory Scale-III; copy and 30 minute delayed recall of the Rey-
214 Osterrieth Complex Figure, Osterrieth & Rey, 1944; word and face recognition on the
215 Warrington Recognition Memory Test, Warrington, 1984), as well as levels of depression
216 and anxiety (the Hospital Anxiety and Depression Scale, Zigmond & Snaith, 1983).

217

218 2.3.1. Real-life event memory procedure

219 The SenseCam (sized 6.5cm wide x 7cm high x 1.5cm long) is built around a PIC
220 18F8722 6 MIPS microcontroller with 128KB of flash memory (Hodges et al., 2006).
221 The SenseCam (see Fig 1a) is worn around the neck and pictures are captured using a fish
222 eye lens. This maximizes the field-of-view and ensures that objects at head height are
223 photographed. Images are captured automatically approximately every 30 seconds.

224

225 INSERT FIGURE 1 ABOUT HERE

226

227 *2.3.2. SenseCam image acquisition and selection*

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

237

238 Following the excursion, images from both patient and control SenseCams were
239 downloaded and reviewed by the researcher and photographs of 20 isolated events were
240 extracted. Events were activities that took place within a single clearly defined spatial
241 context (e.g. the kitchen of a stately home or the rose garden), allowing the visit to be
242 broken down into a linear set of events (one such event can be seen in Fig. 1b). For each
243 event, five sequential images were chosen, except in cases in which two or more images
244 were identical, in which case only one of these images was chosen. To minimise
245 unsystematic variation between patient and control images (e.g. differences in lighting),
246 patients and controls were both shown images of the events taken from the patient's
247 SenseCam, except in cases where substantial differences in viewpoint occurred (e.g.
248 patients and controls in different parts of the same room). This occurred in 21 events
249 (9.5% of all events). In these cases, patients and controls viewed their own respective
250 images of those same events.

251

252

INSERT FIGURE 2 ABOUT HERE

253

254 *2.3.3. SenseCam event memory testing*

255 Memory for events was tested at intervals of i) approximately three hours, ii) one day, iii)

256 one week and iv) three weeks after SenseCam image acquisition. Five different events

257 were selected for each test session. For each event, participants were shown five

258 photographs (as described above). Photographs were presented on a Dell D830 laptop,

259 and measured 125mm (width) by 90mm (height). Presentation times for each photograph

260 were not fixed, and participants were allowed to view the photographs as many times as

261 they wished. For each set of images, participants were initially asked to recall the event

262 pictured (*primary event recall*: 1 point if correct, e.g. “We had just walked into the main

263 hall”; 0 points if incorrect). Then, participants were asked to recall other secondary

264 details associated with that event. This consisted of the events that immediately preceded

265 and followed that event (*contiguous event recall*: 2 points if both correct; 1 point if only

266 one correct; 0 points if neither correct); the participant’s thoughts regarding that event

267 (*thought recall*: 2 points if specifically about that point in time, e.g. “I remember seeing

268 two girls playing with a tennis ball near there, which I thought was odd.”; 1 point for a

269 vague thought not specific to that moment in time, e.g. “I quite liked the museum”; 0

270 points if they failed to recall any thoughts), and sensory information (sounds, smells and

271 temperature) regarding the event (*sensory information*: for each event, a mean score was

272 derived by awarding one point for each of the three types of sensory information present

273 and dividing by three). To ensure that associated detail measures (i.e. contiguous event

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

276

277 2.4. Word-list test

278 A list of 20 words, taken from the word-list learning and interference trials of the Adult
279 Memory and Information Processing Battery (Coughlan & Hollows, 1985), was used to
280 assess verbal memory. Words were presented orally over a minimum of five trials until
281 the participant attained 80% accuracy (i.e. 16 words) at free recall, or until a maximum of
282 10 trials had occurred. After the learning trials, participants were administered a
283 distractor task (odd/even judgement of numbers) for 40s to prevent rehearsal of the
284 words, and limit the effects of working memory on initial recall. Recall of the words was
285 then assessed immediately after the distractor task (40 seconds) and after 30 minutes, one
286 day, one week, and three weeks. Subjects were not forewarned about the delayed probes,
287 but were explicitly requested not to rehearse the material.

288

289 2.5. Serial Reaction Time Test

290 The SRTT was created and run using E-prime (Psychological Software Tools, 2002),
291 which collected reaction times and response data. During the task, four dashes were
292 presented in a line in the centre of the screen, denoting the four possible locations for a
293 cue. The cue was a red asterisk, measuring 0.4cm in diameter and positioned 1cm above
294 one of the lines. Responses were made using four corresponding buttons underneath.
295 These were the keys C, V, B and N, and subjects used the first two fingers of each hand
296 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

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

328

329

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

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

348

349 **3. Results**

350 The demographics of the patient and control groups and their performance on the
351 standard neuropsychological test battery are shown in Table 1. Independent-samples t-
352 tests confirmed that no significant differences existed between the groups on the
353 standardised anterograde memory tests or on the HADS (for all tests, $p > .1$). Patients
354 performed slightly better than controls on the Rey figure copy (Mann-Whitney test:
355 $U=30$, $p < .05$).

356

357 3.1. SenseCam Test

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

361

362 *3.1.1. Primary Event Recall (Figure 3a)*

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

366 $\eta^2_p=.48$), with poorer performance in the patient group. There was a significant delay by
367 group interaction ($F(3,60)=4.1$, $p<.05$, $\eta^2_p=.17$), 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 ($F(3,60)=5.8$, $p<.01$, $\eta^2_p=.22$) and group ($F(1,20)=31.2$, $p<.001$, $\eta^2_p=.61$), with
377 poorer performance overall by patients. There was also a significant delay by group
378 interaction ($F(3,60)=10.7$, $p<.001$, $\eta^2_p=.34$), with planned comparisons revealing
379 significantly greater forgetting in patients than controls between same day and one day
380 delays ($F(1,20)=19.2$, $p<.001$, $\eta^2_p=.49$), 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 ($F(3,60)=9.5$, $p<.001$, $\eta^2_p=.32$) and group ($F(1,20)=12.0$, $p<.01$, $\eta^2_p=.38$), 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

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

438

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

445

446 We investigated whether long-term forgetting rates on the word-list and the ‘ecological’
447 SenseCam task were correlated in all patients. We used percentage retention between
448 initial recall (i.e. 40 seconds for list learning or same day for SenseCam tests) and both
449 one day and three week probes (i.e. the periods over which forgetting was maximal),
450 comparing word-list recall with recall of primary events, contiguous events, thoughts and
451 sensory information. To account for the increased likelihood of a type I error for these
452 eight analyses, results are reported at a Bonferroni-corrected significance level of $p=.006$
453 (i.e. $p=.05/8$). There were no significant correlations between one day retention of the
454 word-list in patients and one day retention on primary event recall ($r(11)=-.01$, $p>.9$; Fig.
455 6a), contiguous event recall ($r(11)=.23$, $p>.4$; Fig. 6b), thought recall ($r(11)=-.27$, $p>.4$;
456 Fig. 6c) or sensory recall ($r(11)=-.57$, $p>.05$; Fig 6d). Three-week retention of the word-
457 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

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

504 We have shown that ALF of real life events can be detected over one day – three weeks
505 following learning in patients with TEA. ALF was apparent for memory of primary
506 events with a large effect size over the entire three week period of observation. ALF of
507 primary events is striking, given the informative nature of the probes. Indeed on this task,
508 controls performed at or near ceiling at same day, one day and three week delays. ALF
509 was equally marked for memory of contiguous events and associated thoughts with large
510 effects over the first day following learning. There was a trend towards accelerated
511 forgetting for memory of sensory information in patients which did not reach
512 significance. This may be a relatively insensitive measure as it is easier to deduce
513 information about sensory details from the visual cues than it is to remember contiguous
514 events or concurrent events. Overall, therefore, there is both a quantitative loss and
515 qualitative deterioration of everyday memories in TEA. The latter indicates that, over
516 time, events that are recalled in TEA become stripped of the associative information that
517 characterises episodic memory (see Tulving, 1972). Whether this reflects impaired
518 consolidation, in which case the memories are lost, or reduced accessibility over time, in
519 which case participants may recognise events given sufficient cueing, is unclear. The
520 detection of ALF in patients with TLE on tests both of recall and recognition (Blake et
521 al., 2000) suggests that the deficits may be due to impaired consolidation; this can be
522 addressed in future studies by also employing tests of recognition. However, regardless of
523 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

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

550

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

568

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

570 We have found that ALF for both real-life events and for a word list is most pronounced
571 over the first day of retention. Three other studies have assessed forgetting over a 24-hour
572 interval in patients with TLE (Martin et al., 1991; Giovagnoli et al., 1995; Bell, Fine,
573 Dow, Seidenberg & Hermann, 2005). Martin et al. (1991) matched patients and controls
574 for initial learning and found impaired retention in patients over 24 hours. Giovagnoli et
575 al. (1995) also matched patients and controls for initial learning but found no difference
576 in retention after one day, three day, six day or thirteen day delays. However, at the
577 thirteen day delay patients and controls still recalled approximately 90% of the stimuli,
578 suggesting that ceiling effects may have influenced the results. In contrast, Bell et al.
579 (2005) did not match groups for learning and subsequently found no difference in
580 forgetting over the first 24 hours. Loftus (1985) has noted that differences in initial
581 learning ability may confound analyses of forgetting rates. Specifically, when groups are
582 mismatched for initial learning, forgetting rates can be underestimated in the lower-
583 performing group as they have less to forget. It is therefore unclear whether patients in
584 the Bell et al. study did indeed show normal forgetting. In the present study, we avoided
585 ceiling effects by using an 80% learning criterion. Although three patients failed to meet
586 our learning criterion, scaling problems cannot account for the present results. The
587 inclusion of these patients would, if anything, have led to an underestimation of
588 forgetting in patients. Furthermore, omission of these poor learners did not affect the
589 findings for recall of events, contiguous events or word-lists. The occurrence of ALF over
590 the first day of retention suggests that an interval of one or a few days should generally be
591 sufficient for the detection of ALF in TEA.

592

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

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

644

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

657

658

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814

815

Acknowledgements

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817 Initiative. We thank John Hodges for his help.

818

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

	<i>TEA Group (n=11)</i>	<i>Control Group (n=11)</i>
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
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

826

Figure Captions

827

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

829

830 Figure 2: Map showing type and location of events.

831

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

838

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

843

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

848

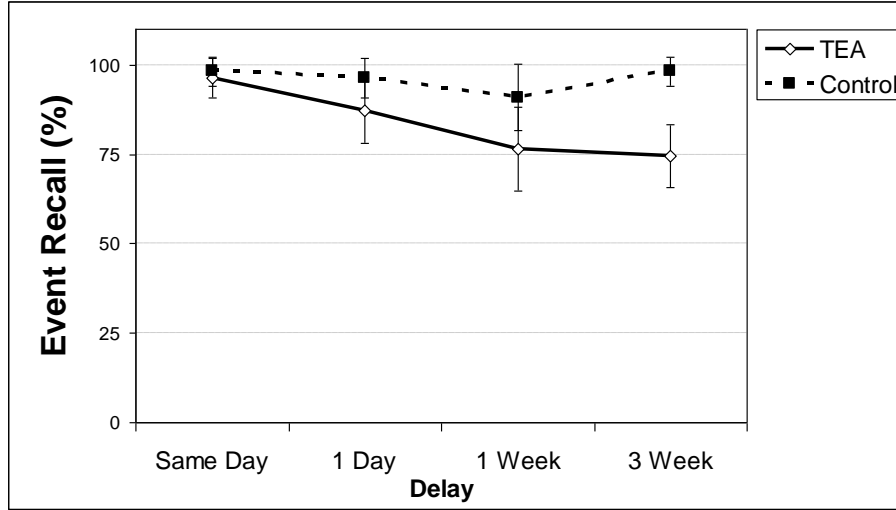
849 Figure 6: Correlations between retention on the list learning and SenseCam tests between
850 40 second or same day respectively, and one day (white triangles and dashed trend-line),
851 or three weeks (red squares and unbroken trend-line) for patients with TEA. Figures show
852 retention of a) primary events; b) contiguous events; c) thoughts; and d) sensory
853 information. x2 = two overlapping data points.

854

855

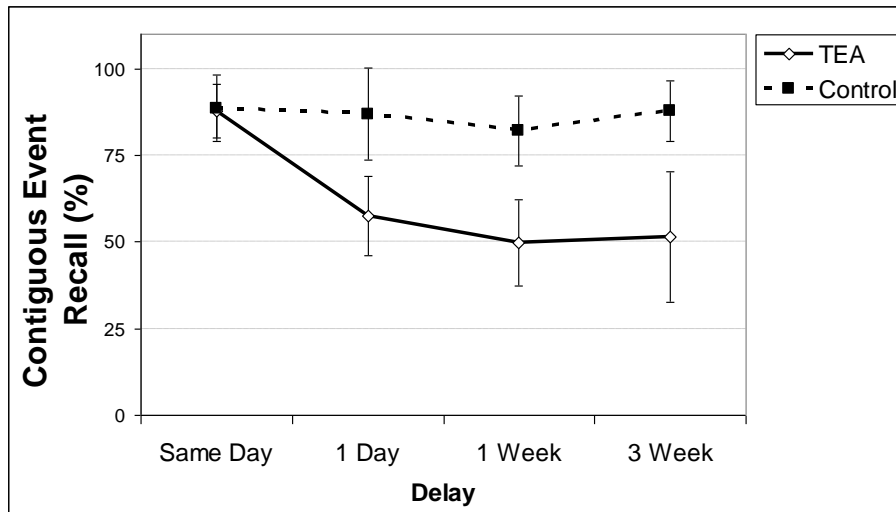
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a.



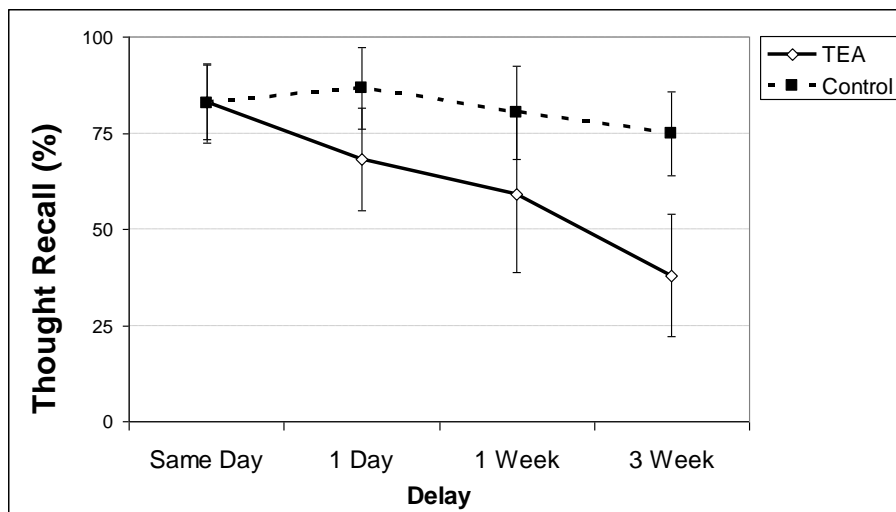
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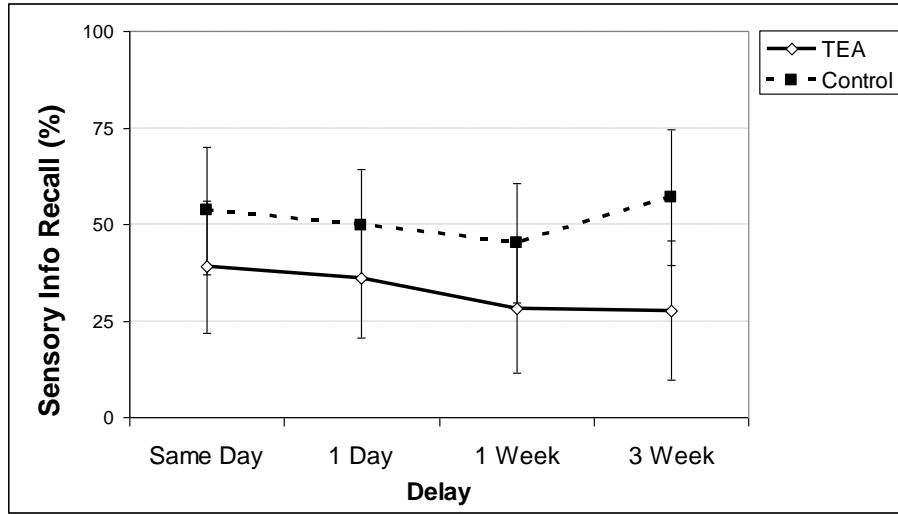
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858

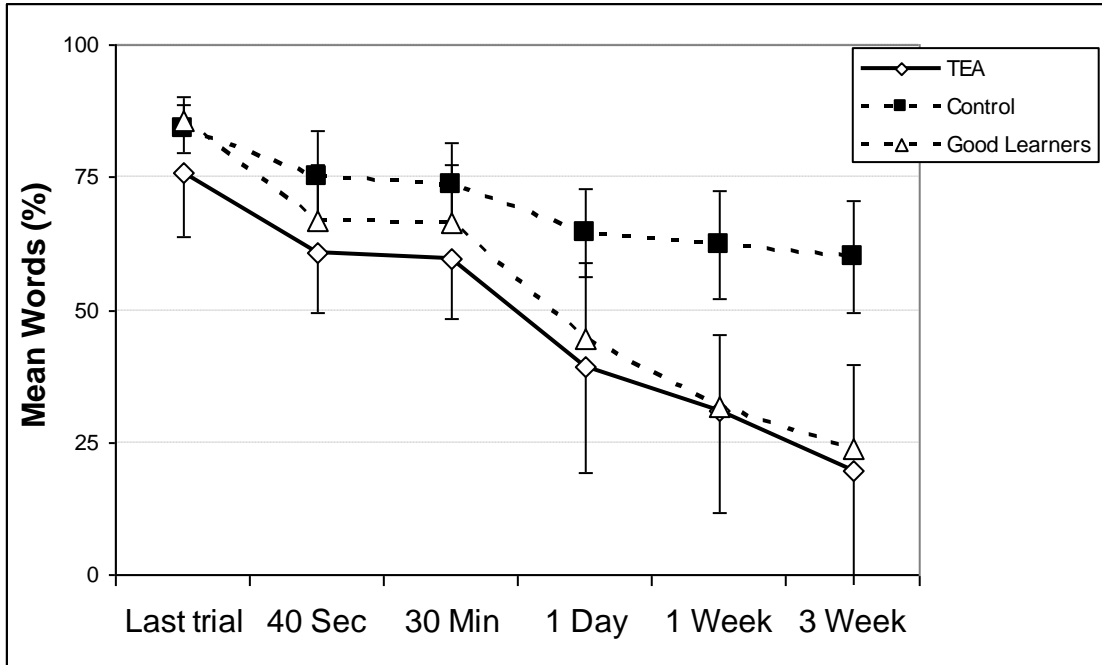
c.





859 d.

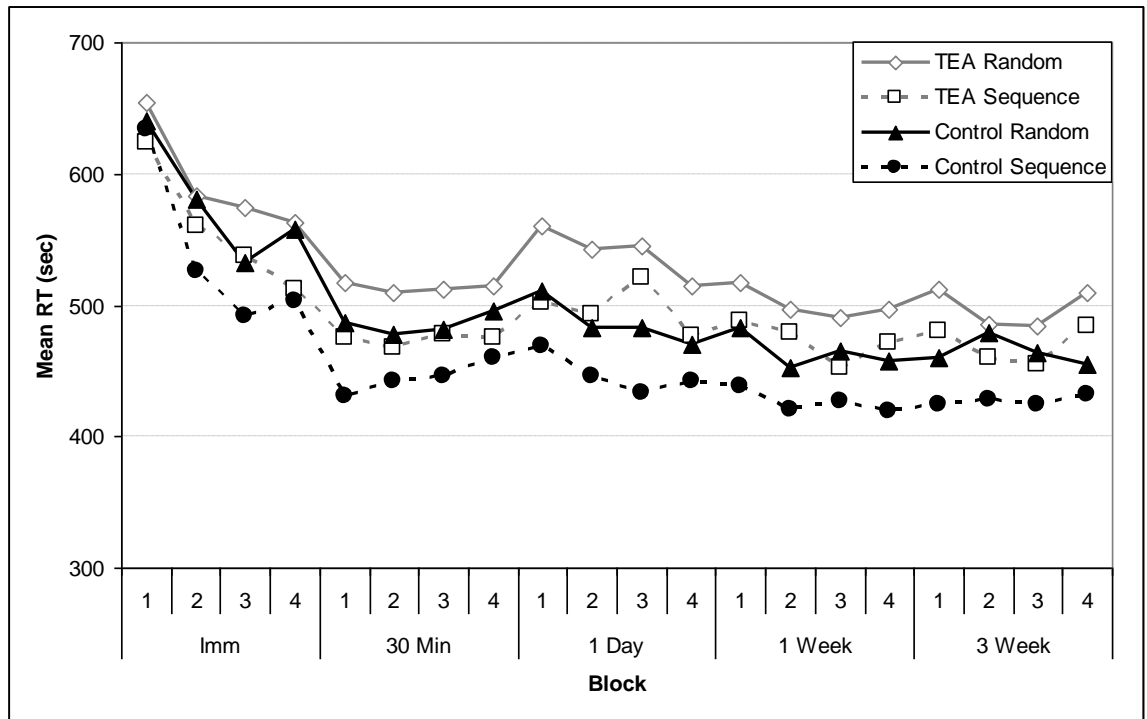
860 Figure 3.



861

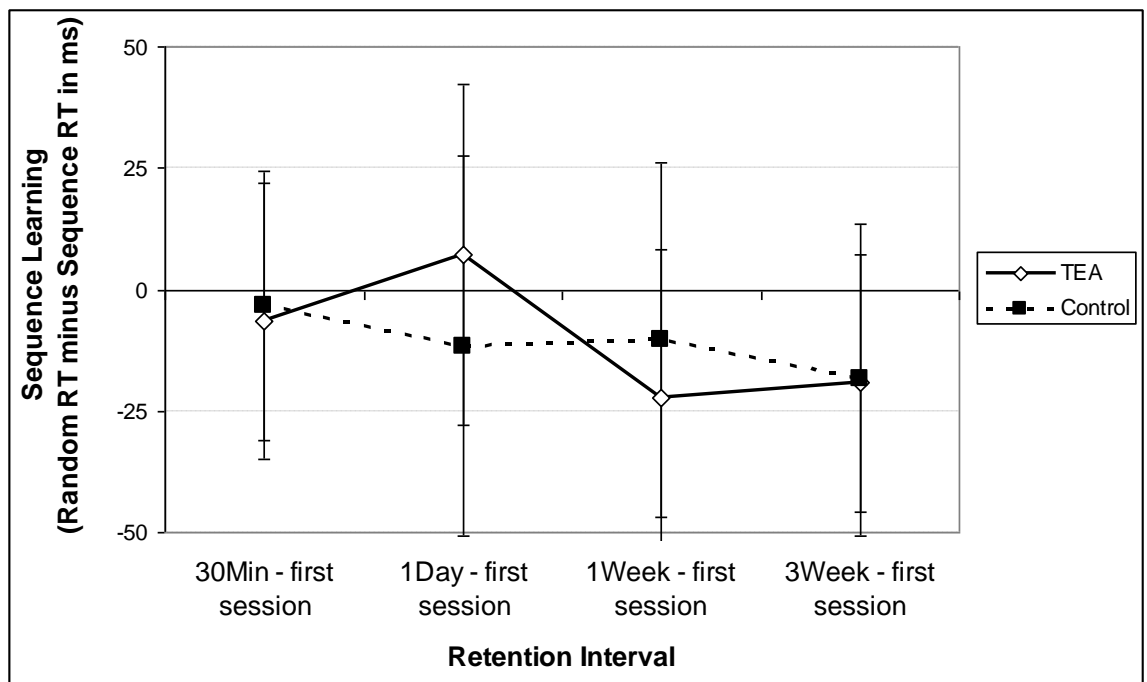
862 Figure 4.

863



864

a.

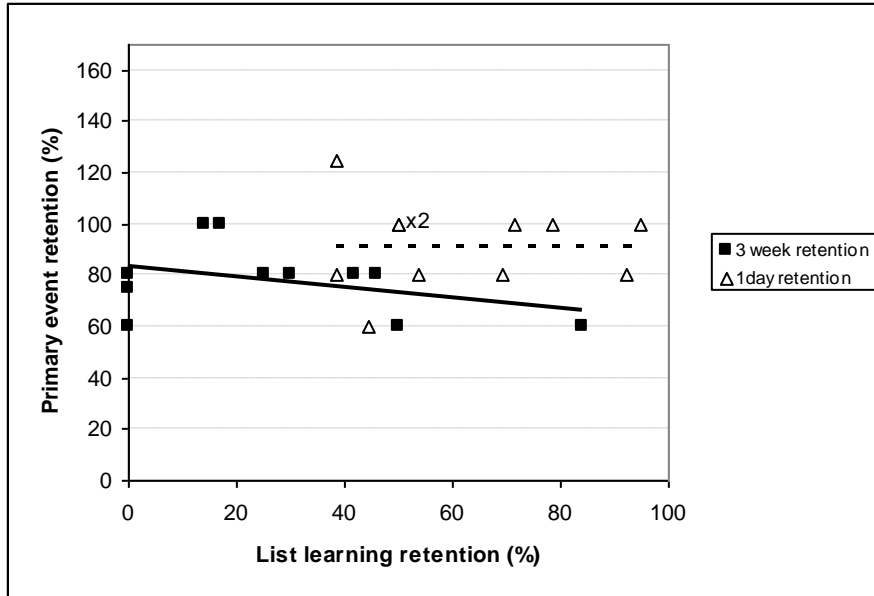


865

b.

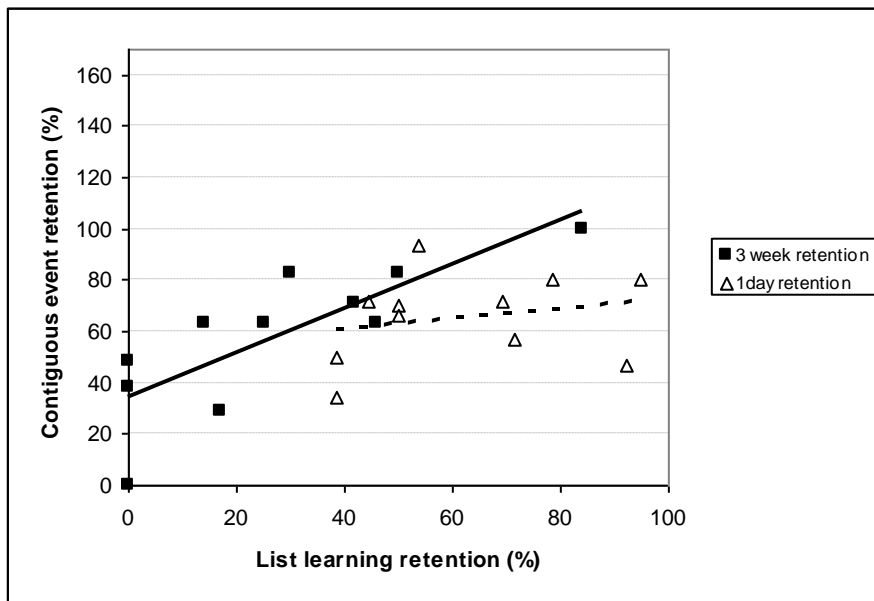
866 Figure 5.

867



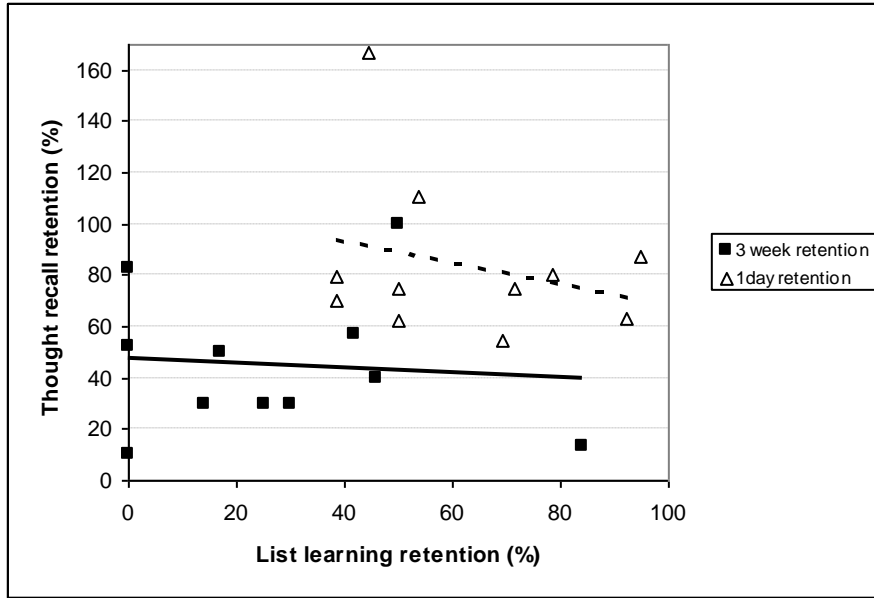
868

a.

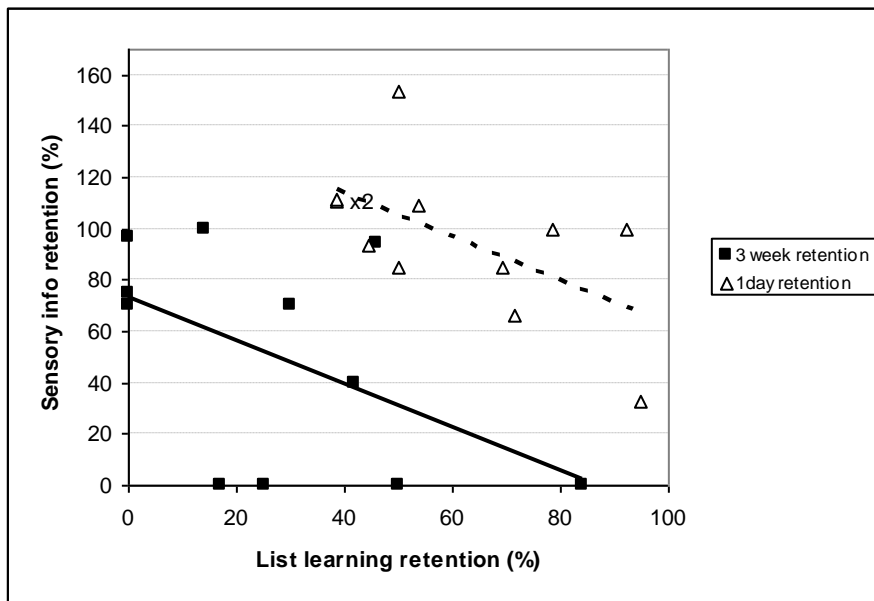


869

b.



870 c.



871 d.

872 Figure 6.