



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Delaying interference enhances memory consolidation in amnesic patients.

Citation for published version:

Dewar, M, Garcia, YF, Cowan, N & Della Sala, S 2009, 'Delaying interference enhances memory consolidation in amnesic patients.' *Neuropsychology*, vol 23, no. 5, pp. 627-634. DOI: 10.1037/a0015568

Digital Object Identifier (DOI):

[10.1037/a0015568](https://doi.org/10.1037/a0015568)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Neuropsychology

Publisher Rights Statement:

This is an Accepted Manuscript of the following article: Dewar, M., Garcia, Y. F., Cowan, N. & Della Sala, S. 1 (2009) "Delaying interference enhances memory consolidation in amnesic patients", *Neuropsychology*. 23, 5, p. 627-634. This article may not exactly replicate the final version published in the APA journal. It is not the copy of record.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.





Published in final edited form as:

Neuropsychology. 2009 September ; 23(5): 627–634. doi:10.1037/a0015568.

Delaying Interference Enhances Memory Consolidation in Amnesic Patients

Michaela Dewar,

Human Cognitive Neuroscience and Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University Edinburgh, Edinburgh, United Kingdom

Yuriem Fernandez Garcia,

Department of Cognitive Neuroscience, Cuban Neuroscience Centre, Havana, Cuba

Nelson Cowan, and

Department of Psychological Sciences, University of Missouri–Columbia

Sergio Della Sala

Human Cognitive Neuroscience and Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh, United Kingdom

Abstract

Some patients with amnesia are able to retain new information for much longer than expected when the time that follows new learning is devoid of further stimuli. Animal work shows that the absence or delaying of interference improves long-term memory consolidation. Our study suggests that this is also true for at least some patients with amnesia. Retention of new verbal material was significantly higher in a sample of patients with amnesia ($N = 12$) when interference occurred at the end of a 9-min delay interval than when it occurred in the middle or at the beginning of the interval. Such findings cannot be accounted for by the mere use of explicit short-term memory rehearsal. Any such rehearsal should have been blocked by the interference, irrespective of interference onset, thus leading to poor retention in all three conditions. The current findings suggest that at least some of the severe forgetting observed in amnesia is the product of a disruption of memory consolidation by immediate postlearning interference.

Keywords

amnesia; memory; consolidation; interference; forgetting

Although patients with amnesia are able to recall new information immediately following learning, they have immense difficulty in doing so following even short delays (Baddeley & Warrington, 1970). It is therefore generally assumed that while short term memory (STM; <1 min) remains intact in patients with amnesia, their ability to form new long term memory (LTM) is greatly impaired (Kopelman, 2002).

The reasons behind this LTM formation impairment are as yet unknown. It is possible that the LTM formation system is entirely defective. However, there is the alternative possibility that some new LTM formation can still take place, but that further stimuli, which are pervasive in everyday life and clinical testing, profoundly interfere with such process. Given that new

memory traces have been found to be weak and susceptible to interference (cf Dudai, 2004), an interference hypothesis for amnesia may not be improbable. Importantly, animal work has elucidated that new memory traces strengthen and become less vulnerable to interference over time (Dudai, 2004; Wixted, 2004). A delay in the onset of postlearning interference thus results in enhanced LTM formation in neurologically intact neural systems (Dudai, 2004).

Whether the delaying of interference might also alleviate LTM formation in patients with amnesia is as yet unknown, and was therefore the main question of the present study.

Anecdotal reports hint that a complete absence of postlearning stimuli might enhance memory in some patients with amnesia (Drachman & Arbit, 1966). Scoville and Milner (1957) for example report that all their patients with severe amnesia, including the famous amnesiac HM, *'were able to retain a three-figure number or a pair of unrelated words for several minutes, if care was taken not to distract them in the interval. However, they forgot the instant attention was diverted to a new topic.'* (p. 15).

Encouraged by such anecdotal evidence, Cowan, Beschin, and Della Sala (2004) sought to examine empirically whether patients with amnesia would be able to retain new verbal material following longer periods of minimal distraction. Their paradigm was inspired by a classic study on cockroaches in which shock-avoidance retention was tested following a 1–3 hr delay of either further activity or inactivity (i.e., in a small box lined with tissue that curtailed motor activity; Minami & Dallenbach, 1946). Whereas 1 hr of inactivity led to 89% savings (i.e., reduced the number of trials needed to relearn the avoidance), further activity led to only 59% savings.

Cowan et al. (2004) presented 6 patients with severe amnesia with 15 words. The patients were subsequently asked to recall as many of the words as they could immediately following presentation, as well as after a 10-min interval. This delay interval either simulated a standard memory assessment in that it was filled with further cognitive testing, or it remained unfilled, meaning that the patient was left alone in the quiet, darkened testing room. Whereas two of the patients were unable to recall any of the words in either condition, four patients showed substantially greater word list retention following the unfilled (49%) than the filled condition (14%). A comparable benefit occurred for the control group, whose mean percentage retention was 46% and 74% in the filled and the unfilled conditions respectively. Nevertheless, this benefit of minimizing interference would not be expected in patients with amnesia unless they have a residual, previously hidden, memory capability.

In order to examine whether such findings would also be elucidated following an even longer delay, Cowan et al. (2004) replicated the experiment on the same participants using a 1-hr delay interval, with prose passages instead of word lists as to-be retained material. As in the first experiment four of the six (the same as previously) patients benefited significantly from the unfilled 1-hr delay interval, the group mean percentage retention being 7% following the filled interval and 79% following the unfilled delay interval. (The control group mean percentage retention was 79% and 89%, following the filled and unfilled delays, respectively).

Why some patients benefited from the minimization of interference while others did not is unclear, but differences in lesion loci and etiology are likely candidates (Cowan et al., 2004). In order to minimize individual differences in etiology and lesion loci, Della Sala, Cowan, Beschin, and Perini (2005) replicated Cowan et al. (2004) prose memory study with a sample of patients diagnosed with amnesic mild cognitive impairment (aMCI; Petersen et al. 1999). As in the study by Cowan et al. (2004) the patients performed significantly better following the unfilled (55%) than the filled delay interval (20%). (Age and education matched controls showed a group mean percentage retention of 80% following the filled condition and 89% following the unfilled condition).

This remarkable memory improvement in patients with amnesia following an unfilled delay interval led Cowan et al. (2004) and Della Sala et al. (2005) to propose that the severe forgetting in least some patients with amnesia is the product of a high susceptibility to retroactive interference (RI). They hypothesized that patients with amnesia do not forget inevitably with the passage of time, but because the information filling such passage of time interferes with vital memory processes. The idea that patients with amnesia may be highly susceptible to interference was postulated in the 1970s by Warrington and Weiskrantz (1970, 1974). However, they focused on a proactive interference hypothesis, which they later rejected (Warrington & Weiskrantz, 1978; Weiskrantz, 1982). Prior to Cowan et al.'s (2004) work, memory interference from postlearning activity in patients with amnesia had only been considered within the STM domain.

As argued above, it is traditionally assumed that the ability of patients with amnesia to form new LTM is greatly impaired (Kopelman, 2002), and that new information is only retained for very brief intervals within patients' intact STM (Baddeley Warrington, 1970). According to this traditional theory of amnesia, new information is lost rapidly as soon conscious rehearsal ceases to take place, often because other stimuli have diverted the patient's attention from conscious rehearsal (Scoville & Milner, 1957; Milner, 1968; Ogden, 1996). This traditional account thus posits that postlearning information interrupts conscious STM rehearsal in patients with amnesia.

If this were the case, the memory improvement observed following the unfilled delay in Cowan et al. (2004) and Della Sala et al. (2005) should have been the mere product of uninterrupted STM rehearsal. However this appears unlikely for several reasons. First, the initial delayed recall came as a surprise, meaning that the patients had little if no incentive to explicitly and continuously rehearse the material for up to an hour. Nonetheless, percentage retention in this initial trial was not lower than that in the subsequent trials. Furthermore, the to-be-retained information in two of the three experiments by Cowan et al. (2004) and Della Sala et al. (2005) was a prose passage consisting of a much larger quantity of information than can be rehearsed within the traditional time-limited working memory. If explicit rehearsal were the only cognitive process underlying the memory improvement, patients should have only recalled as much information as can be actively rehearsed in STM. Finally, two patients in the Cowan et al. (2004) study were observed to be sleeping (identified by loud snoring, a state in which conscious rehearsal should be impossible) during some hour-long unfilled delay intervals. However, they benefited from the unfilled delay interval as much as on other trials, and as much as other patients did.

It thus appears that the minimization of postlearning information in patients with amnesia does not simply allow for uninterrupted STM rehearsal, but might in fact enable a partially spared LTM process to function.

Over a century ago Müller and Pilzecker (1900), who examined forgetting in the neurologically intact population, proposed that the minimization of postlearning interference enhances memory consolidation in the neurologically intact human brain. In their Experiment 34, they presented participants with a to-be-retained syllable lists. A further syllable list was subsequently introduced either 17 s or 6 min following the learning of the to-be-retained syllable list. Retention was found to increase from 28% in the 17-s condition to 49% in the 6-min condition. Müller and Pilzecker (1900) argued that the first syllable list could consolidate thoroughly during the 6-min interval, thus being less susceptible to the subsequent interfering effect of the interpolated syllable list. It was therefore reasoned that new memory traces are initially fragile and vulnerable to retroactive interference but strengthen, that is, consolidate, over time (Dewar, Cowan, & Della Sala, 2007).

Further early behavioral work on such consolidation interference hypothesis was undertaken by Skaggs (1925). Participants in his study were presented with a chess board containing five chessmen, whose positions the participant had to remember after a 5-min delay. During this interval simple algebra problems were interpolated at one of four onset times. In keeping with the consolidation interference hypothesis, the average number of errors was highest when the interpolated task occurred immediately following learning, but leveled thereafter.

More recent evidence for such a consolidation interference hypothesis comes from behavioral animal neuroscience research. Izquierdo, Schröder, Netto, and Medina (1999), for example, trained rats not to step off a platform by administering a mild shock if they did so. The rats were then allowed to explore a novel environment for 2 min either 1 hr or 6 hr following learning. When tested 24 hr after initial learning, memory was impaired in those rats who had explored the new environment 1 hr postlearning, but not in those who had explored the new environment 6 hr postlearning.

Recent animal neuroscience studies on the effect of protein synthesis inhibitors on memory have provided further strong evidence for a time-dependent effect of interference on consolidation in the neurologically intact brain (Agranoff, Davis, & Brink, 1966; Dudai, 2004). Protein synthesis inhibitors, usually antibiotics or toxins, are known to interfere with the neural processes associated with memory formation in animals (Agranoff et al., 1966; Dudai, 2004). It has been widely shown that retention of recently learned material is low if a protein synthesis inhibitor is introduced immediately following learning. However, retention increases steadily with augmenting delay in the introduction of the protein synthesis inhibitor, a finding that once again elucidates a decrease in the susceptibility to interference over time, and thus a time-dependent memory strengthening process.

Such findings strongly suggest that interference of various types, occurring immediately or shortly following the learning of to-be-retained information, has a detrimental effect on the consolidation of the to-be-retained material in neurologically intact neural systems.

It should be noted that another form of interference must be described. When interference stimuli are highly similar to the to-be-retained material, for example, if the first word of two word pairs is identical, such as *tree-glass—tree-train*, a detrimental effect is also observed when the interfering stimuli is placed immediately prior to delayed recall (e.g., Postman & Alper, 1946; Newton & Wickens, 1956; see Wixted, 2004 for a review). In this case recent interference stimuli are hypothesized to interfere with LTM retrieval by competing for retrieval with the highly similar to-be-recalled material (Skaggs, 1933; Postman & Alper, 1946; Wixted, 2004; Dewar et al., 2007). We did not examine this second type of interference.

In the present study we used a behavioral variant of the aforementioned neuroscience paradigm (Agranoff et al., 1966; Dudai, 2004) to examine whether minimization of immediate postlearning interference enhances LTM consolidation in patients with amnesia. Participants were presented with a word list, which they were asked to recall immediately following presentation, as well as after a 9-min delay, which could include interpolated stimuli during the first, the middle, or the last 3 min of the 9-min delay.

Maintenance of new information in STM by definition has to be continuous, and one would expect it to be disrupted by subsequent interference (Baddeley & Hitch, 1974; Baddeley, 1986). Thus, if minimizing interference in patients with amnesia did improve memory, yet solely via STM maintenance, new information should be lost as soon as the unfilled interval was followed by interference, regardless of its temporal onset. On the other hand, if minimizing interference following learning in patients with amnesia allowed for enhanced consolidation, then at least some retention might be observed even after interference, provided that this

interference were preceded by a sufficient period of minimal interference. Moreover, one would expect retention to increase as a function of the temporal onset of interference.

An alternative possibility would be interference with retrieval, as noted above. The interference stimuli used in this study were not highly similar to the to-be-retained word list material. Therefore any interference with retrieval should have been greatly minimized. Nonetheless, it perhaps cannot be excluded a priori that even non-highly similar material could interfere with LTM in amnesic patients. Given the above retrieval interference findings, we thus assumed that if the benefit from minimal interference in patients with amnesia came from enhanced LTM retrieval, retention should be poorer when interference stimuli are presented immediately prior to recall than when they are presented midway through the delay interval.

Materials and Method

Participants

We tested 12 patients with amnesia and 12 age- and IQ-matched controls (see Table 1). All participants had a normal neurological examination, and the controls were healthy as evinced by a normal medical history. The patients were diagnosed with aMCI according to Petersen et al.'s (1999) operational criteria: (a) a memory complaint corroborated by an informant, (b) objective memory impairment, (c) otherwise normal general cognitive function, (d) intact activities of daily living, and (e) an absence of dementia.

In line with these criteria all included patients performed poorly on tests of LTM (delayed word list recall; delayed figure recall), yet within the normal range on tests of STM (digit span; spatial span) and other cognitive function (verbal comprehension; verbal fluency) (see Table 1). Moreover, all patients had a Clinical Dementia Rating Scale (CDR) score of 0.5, indicating a profound deficit in memory as compared to all other cognitive domains and activities of daily living. Furthermore, all patients scored $\geq 24/30$ on the Mini-Mental State Examination (MMSE), and MMSE points were mainly lost on the memory component (recall subscore) as opposed to on the non-memory components. Thus, the patients' cognitive deficits were characterized by isolated dense amnesia.

Procedure

All participants underwent four trials, in each of which they were presented with a new word list consisting of 15 standardized words (Snodgrass & Vardewart, 1980). The digitally recorded word lists were presented to the participants aurally via headphones at a rate of one word every 2 s using MATLAB (The Maths Works Inc). Participants were asked to try and remember as many of the words as possible for subsequent immediate free recall. No warning regarding subsequent *delayed* recall was provided. It should be noted however that while delayed recall was likely to come as a surprise in the first trial, participants may have expected delayed recall during later trials.

The critical manipulation was the temporal position of 3-min interference within the 9-min delay interval preceding delayed recall (see Figure 1): Interference occurred during the first (*early*), the middle (*mid*), or the last (*late*) third of the otherwise unfilled delay interval. Moreover, a control condition (*unfilled*), in which the entire 9-min delay interval remained unfilled, was also included. During the unfilled periods, the participants rested alone in the quiet, darkened testing room, which was free of any interfering material.

Two opposite orders of the conditions were used, *early-mid-late-unfilled*, and the reverse.

The interference task involved picture naming. Forty-five gray-scaled line drawings (Snodgrass & Vanderwart, 1980) with superimposed words were presented to the participants

(one picture-word pair every 4 s) on a computer screen via MATLAB (The Maths Works Inc). Participants were instructed to name each picture as fast as possible without reading the superimposed word. Picture naming was utilized in order to minimize any potential attempted conscious verbal rehearsal of the word list material. To increase the cognitive demand, in 1/3 of the stimuli the name did not match the picture but was in the same semantic category (e.g., a picture of lips and the word “nose”). The residual 2/3 of the stimuli were congruent (e.g., a picture of a cat and the word “cat”).

A pilot study on 12 neurologically intact volunteers indicated that the interference stimuli used in the three conditions did not differ in cognitive demand, neither when measured objectively as the number of pictures named correctly, nor subjectively via participant feedback.

Statistical Analyses

As in Cowan et al. (2004) and Della Sala et al. (2005) a proportion retention score was computed for each participant for each of the four trials by dividing the number of correct words recalled at delayed recall by the number of correct words recalled at immediate recall in the same trial. Such procedure controls for potential individual and group differences as well as any intertrial variation at immediate recall.

A mixed factor analysis of variance (ANOVA) with within-subjects factor Condition (unfilled vs. early vs. mid vs. late) and between-subjects factor Group (patients vs. controls) was run to examine the effects of interference and its temporal position on retention in the patient and the control sample. Further examination of the data was undertaken via Newman–Keuls pairwise comparisons and ANOVAs.

The unfilled condition and early condition either occurred in the first or the last trial depending on condition order group. Thus, those receiving the unfilled condition in the first trial received the early condition in the last trial and vice versa. In the first trial participants had very little reason to expect delayed recall. It was therefore unlikely that any explicit rehearsal would have taken place during this trial. In order to examine whether proportion retention in the unfilled condition differed between the two condition order groups, a one way ANOVA was conducted. The same analysis was also performed on proportion retention in the early condition.

Pearson correlations were utilized to examine potential trade-off effects between memory and interference task performance. Potential intrusion effects from interference stimuli were assessed via repeated measures ANOVAs.

The alpha level was set to 0.05 for all analyses.

Results

Memory Performance

Figure 2 shows that the interference as well as its temporal position had a substantial effect on word list retention in the patients. This effect was also observed in the control group, albeit to a much lesser extent as is shown in Figure 2 and by a highly significant Condition \times Group interaction, $F(3, 66) = 6.22, p < .001$. This interaction remained highly significant even when only the three interference conditions (early, mid, late) were included in the analysis, $F(2, 44) = 7.32, p < .002$.

Effect of interference—Both groups performed significantly better when interference was absent (unfilled condition – $M_{\text{Patients}} = 0.55, M_{\text{Controls}} = 0.76$) than when it occurred at the beginning of the delay interval (early condition – $M_{\text{Patients}} = 0.10, M_{\text{Controls}} = 0.59$). However, this increase in retention, which was observed in 11 out of the 12 patients (see Table 2), was

significantly larger for the patients than the controls, $F(1, 23) = 11.501, p < .003$. Retention was also significantly higher in both groups when interference was absent than when the onset of interference was delayed by 3 min (mid condition – $M_{\text{Patients}} = 0.20, M_{\text{Controls}} = 0.54$). This rise in retention, which was shown in 10 out of the 12 patients, did not differ significantly between groups.

Effect of temporal position of interference—As shown in Figure 2, the patients retained significantly more word list material when the temporal onset of interference was delayed by 6 min ($M = 0.48$) than when it was delayed by 3 min, or when interference occurred at the beginning of the delay interval. No significant effects of temporal position of interference were revealed in the controls.

Some variability in performance patterns was observed in the patients across the conditions. In an important finding, however, *all* 12 patients showed the memory improvement from the early to the late interference condition (see Table 2). This improvement was most notable in the 8 patients who were unable to recall any words following early interference. Furthermore, 8 out of the 12 patients showed the improvement from the mid to the late condition (see Table 2).

The observed benefit of a delay in interference of at least 6 min thus appears to be a very robust one.

Main effect of group—Figure 2 further illustrates that the groups differed substantially with early interference, but became much more similar if interference was omitted (unfilled condition) or delayed. Nonetheless, a highly significant main effect of Group was revealed, $F(1, 22) = 45.067, p < .0001$, and retention was significantly higher for the controls than the patients in all four conditions ($F(1, 23) = 12.64, p < .002$; $F(1, 23) = 10.422, p < .004$; $F(1, 23) = 12.878, p < .002$; $F(1, 23) = 81.676, p < .002$, for the unfilled, late, mid and early conditions respectively).

Order of conditions and first trial performance—Proportion retention in the unfilled condition did not differ significantly between those patients who received the unfilled condition first ($M_{\text{Unfilled}} = 0.51$) and those patients who received the unfilled condition last ($M_{\text{Unfilled}} = 0.55$). Neither did proportion retention in the early condition differ significantly between those patients who received the early condition first ($M_{\text{Early}} = 0.12$) and those who received the early condition last ($M_{\text{Early}} = 0.05$).

Interference Task Performance

Trade-off between memory and interference performance—In order to examine whether the patients' improvement in retention from the early to the late condition may have been the product of a trade-off between memory and interference task performance levels, a correlation was run between the slopes of these two measures across conditions. This correlation was not significant ($r = -.03, p = .350$) indicating no significant trade-off between memory and interference task performance.

Intrusions from interference task stimuli at retrieval of word lists—The number of intrusions from the 45 interference task stimuli was extremely low, the mean number of intrusions per condition being 0.31 (SEM = 0.20) for the patients with amnesia and 0.17 (SEM = 0.07) for the controls, and did not differ significantly between the two groups. Moreover, an analysis of intrusions from interference task stimuli at retrieval of word list stimuli indicated no significant difference in the number of such intrusions between conditions in the patients ($M_{\text{Early}} = 0.08, M_{\text{Mid}} = 0.58$ and $M_{\text{Late}} = 0.25$).

Discussion

The patients with amnesia retained significantly more word list material when the 9-min delay interval was unfilled than when an interfering task was introduced directly following immediate recall. This is in agreement with Cowan et al.'s (2004) and Della Sala et al.'s (2005) recent findings.

Most important however is the novel finding that the amnesic patients' retention was also significantly higher when the interference task was delayed by 6 min (late condition) than when occurred immediately (early condition) or 3 min following immediate recall (mid condition).

The improvement from the early to the late condition, which was shown in all 12 patients, and which was most noteworthy in the 8 patients who were unable to recall any words following early interference, clearly demonstrates that the patients with amnesia were able to retain new verbal material in the presence of interference *if* the onset of this interference was delayed by at least min.

Such finding provides strong evidence that the patients did not simply benefit from the absence of immediate postlearning interference due to conscious STM rehearsal. The early, mid and late conditions all included the same amount of interference, disrupting STM rehearsal. Mere rehearsal, in the absence of any LTM formation, should have therefore only resulted in a memory improvement in the unfilled condition, in which interference was entirely absent. Retention in the early, mid and late conditions should have been equally poor. However, as shown in Figure 2, retention improved substantially in the late condition compared with the early and mid conditions.

This improvement cannot be dismissed as a trade-off between memory and interference task performance levels, inasmuch as the slopes of these two measures across conditions were uncorrelated. Further evidence against a STM rehearsal account comes from the comparison of the two condition order groups' retention in the unfilled and early conditions, which occurred in the first trial and last trial respectively, or vice versa. Delayed recall was unexpected in the first trial, meaning that rehearsal was unlikely to have occurred then. Nonetheless, patients for whom the unfilled trial came first, performed as well in this condition as did those patients, for whom the unfilled trial came last. The same was true for the early condition.

Our data therefore indicate that it was LTM that was improved substantially in the present patients with amnesia via a period of minimal interference.

It is unlikely that the memory improvement demonstrated in these patients was the product of uninterrupted LTM retrieval. As argued above, a high similarity between to-be-retained and interference stimuli is required for an interference effect to occur at LTM retrieval in neurologically intact individuals (Skaggs, 1933; McGeoch & Nolen, 1933; Mensink & Raaijmakers, 1988; Anderson & Bjork, 1994; see also Wixted, 2004). Moreover, the observed response pattern is not in line with that predicted by previous retrieval studies on the temporal onset of highly similar interference (e.g., Postman & Alper, 1946; Newton & Wickens, 1956). These studies elucidated poorer memory for to-be-retained material when interference occurred immediately prior to recall than when interference occurred halfway through the delay interval, the opposite pattern from that demonstrated in our study.

Moreover, a retrieval account would predict a larger number of intrusions from the interference stimuli in the early than the late condition. However, the analysis of intrusions from interference stimuli at retrieval of word list stimuli indicated no significant difference in the number of such intrusions between conditions. In fact, the mean number of intrusions from the 45 interference stimuli per condition was extremely low (< 1), suggesting that interference stimuli did not

interfere with the retrieval of word list stimuli. An LTM retrieval hypothesis would therefore run into difficulty in accounting for our results.

This is not the case however for the consolidation hypothesis, the predictions of which are in close accordance with our data.

The aforementioned behavioral and pharmacological work on animals has revealed a time-dependent memory consolidation process, during which a steady increase in stability and thus resistance to interferences is observed over time (Dudai, 2004). We thus predicted that if minimal interference allowed for enhanced consolidation in amnesic patients, a similar response pattern should be observed in our behavioral analogue.

Figure 2 demonstrates that this was indeed the case. Our data therefore suggest that new memory traces can become consolidated in at least some amnesic patients, but that postlearning interference disrupts this process substantially. As found in the animal literature, this interruption is most detrimental when the interference occurs directly following new learning, that is, when the new memory trace has not yet had a chance to consolidate, but decreases with augmenting delay in interference. Why the controls' performance was not at its worst in the early condition is unclear. It is possible that some controls attempted to rehearse during the interference task, and that such attempted rehearsal concealed a temporal gradient of interference in this group.

Unlike protein synthesis inhibitors, "behavioral" interference, such as the one applied in the present study, is the norm in every day life. As demonstrated in the present study as well as previous work, such interference has a detrimental effect on memory in neurologically intact individuals (Müller & Pilzecker, 1900; Skaggs, 1925; Dewar et al., 2007). However, the present finding as well as the work by Cowan et al. (2004) and Della Sala et al. (2005) show that such an effect is extremely mild when compared to that observed in patients with amnesia. Indeed, it is very evident from every day life that neurologically intact individuals are easily able to consolidate new memories in the midst of much immediate interfering information. In patients with amnesia however, this ability appears to have broken down.

The reasons behind such breakdown in normal consolidation ability remain to be examined. One possibility is that resources required for the consolidation of new memory traces are greatly reduced in patients with amnesia. Wixted (2004) argues that in neurologically intact individuals the resources required for consolidation are not unlimited. He hypothesizes that when to-be-retained stimuli are followed by further information, resources have to be divided between the processing of the to-be-retained stimuli as well as the processing of further information. This division of resources is postulated to lead to the small drop in retention observed in neurologically intact individuals when performance following a filled delay is compared with that following an unfilled delay.

A considerable depletion of such consolidation resources in patients with amnesia could render the consolidation mechanism unable to process more than a few new units of information at any one time. Newly learned information may thus not be consolidated properly if further information, competing for greatly limited resources, follows immediately. If however the onset of further information is delayed, there may be sufficient resources for the newly learned information to be adequately strengthened.

It should be noted that the consolidation theory has been criticized for its apparent inability to account for instances of memory recovery following longer delays or cues (cf. Spear & Riccio, 1994). Given that no further, extensive free recall or cued-recall test was administered in the present study, it is unknown whether any of the previously nonrecalled material may have been

retrievable under such conditions. Moreover, a null finding in further tests still could not remove all doubt in this regard.

Also, a positive finding would not necessarily speak against a consolidation account of our data. Immediate postlearning information may not block all consolidation of newly learned material in amnesic patients. It could simply lead to a greatly weakened memory trace that is only retrievable via specific reminders or contextual cues (cf. Dudai, 2004; Squire, 2006).

The present data provide a striking behavioral demonstration of time-dependent memory strengthening, that is, consolidation, in the human brain, and show for the first time that such a process is possible in at least some amnesic patients so long as new learning is not immediately followed by further information.

At least for the degenerative amnesia considered here, our findings therefore permit a novel theoretical account, in which the severe forgetting in amnesia stems from disruption of the consolidation process by subsequent information. We hypothesize that such disruption of the consolidation process by subsequent information may be the consequence of a depletion of consolidation resources in patients with amnesia. This depletion of consolidation resources could be associated with the synaptic changes within the hippocampus that are hypothesized to occur in the very early stages of Alzheimer's disease (Selkoe, 2002), of which aMCI is frequently a harbinger.

Acknowledgments

A European Commission Alfa program grant and a Royal Society bilateral (U.K.-Cuba) project grant to SDS supported the data collection MD's salary is currently granted by the Alzheimer's Research Trust. We are extremely grateful to all patients and control participants who volunteered to take part in this study.

References

- Agranoff BW, Davis RE, Brink JJ. Chemical studies on memory fixation in goldfish. *Brain Research* 1966;1:303–309. [PubMed: 5955961]
- Anderson, MC.; Bjork, RA. Mechanisms of inhibition in long-term memory: A new taxonomy. In: Dagenbach, DD.; Carrn, T., editors. *Inhibitory processes in attention, memory and language*. New York: Academic Press; 1994. p. 265-326.
- Baddeley, A. *Working memory*. Oxford: Clarendon Press; 1986.
- Baddeley, A.; Hitch, GJ. Working memory. In: Bower, GA., editor. *The Psychology of Learning and Motivation*. New York: Academic Press; 1974. p. 47-89.
- Baddeley AD, Warrington EK. Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behaviour* 1970;9:176–189.
- Carlesimo GA, Caltagirone C, Gainotti G. The Mental Deterioation Battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *The Group for the Standardization of the Mental Deterioation Battery*. *European Neurology* 1996;36:378–384. [PubMed: 8954307]
- Cowan N, Beschin N, Della Sala S. Verbal recall in amnesic patients under conditions of diminished retroactive interference. *Brain* 2004;27:825–834. [PubMed: 14749294]
- Della Sala S, Cowan N, Beschin N, Perini M. Just lying there, remembering: Improving recall of prose in amnesic patients with mild cognitive impairment by minimizing interference. *Memory* 2005;13:435–440. [PubMed: 15948630]
- De Renzi E, Faglioni P. Normative data and screening power of a shortened version of the Token Test. *Cortex* 1978;14:41–49. [PubMed: 16295108]
- Dewar MT, Cowan N, Della Sala S. Forgetting due to retroactive interference: A fusion of Müller and Pilzecker's (1900). early insights into forgetting and recent research on anterograde amnesia. *Cortex* 2007;43:616–634. [PubMed: 17715797]

- Drachman DA, Arbit J. Memory and the hippocampal complex. *Archives of Neurology* 1966;15:52–61. [PubMed: 5937496]
- Dudai Y. The neurobiology of consolidation, or, how stable is the engram? *Annual Review of Psychology* 2004;55:51–86.
- Folstein MF, Folstein SE, McHugh PR. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research* 1975;12:189–198.
- Gonzalez HM, Mungas D, Reed BR, Marshall S, Haan MN. A new verbal learning and memory test for English-and Spanish-speaking older people. *Journal of the International Neuropsychological Society* 2001;7:544–555. [PubMed: 11459106]
- Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging dementia. *British Journal of Psychiatry* 1982;140:566–572. [PubMed: 7104545]
- Izquierdo I, Schröder N, Netto CA, Medina JH. Novelty causes time-dependent retrograde amnesia for one-trial avoidance in rats through NMDA receptor- and CaMKII-dependent mechanisms in the hippocampus. *The European Journal of Neuroscience* 1999;11:3323–3328. [PubMed: 10510197]
- Kopelman MD. Disorders of memory. *Brain* 2002;125:2152–2190. [PubMed: 12244076]
- McGeoch JA, Nolen ME. Studies in retroactive inhibition IV. Temporal point of interpolation and degree of retroactive inhibition. *The Journal of Comparative Psychology* 1933;15:407–417.
- Mensink GJ, Raaijmakers JGW. A model for interference and forgetting. *Psychological Review* 1988;95:434–455.
- Milner B. Disorders of memory after brain lesions in man. *Neuropsychologia* 1968;6:175–179.
- Milner B. Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin* 1971;27:272–277. [PubMed: 4937273]
- Minami H, Dallenbach KM. The effect of activity upon learning and retention in the cockroach. *The American Journal of Psychology* 1946;59:1–58.
- Müller GE, Pilzecker A. Experimentelle Beiträge zur Lehre vom Gedächtniss. *Zeitschrift für Psychologie Ergänzungsband* 1900;1:1–300.
- Newton JM, Wickens DD. Retroactive inhibition as a function of the temporal position of the interpolated learning. *Journal of Experimental Psychology* 1956;51:149–154. [PubMed: 13295503]
- Ogden, J. Marooned in the moment. In: Ogden, J., editor. *Fractured minds. A case-study approach to clinical neuropsychology*. New York: Oxford University Press; 1996. p. 41-58.
- Osterrieth PA. Le test de copie d'une figure complexe. *Archives de Psychologie* 1944;30:206–356.
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment. Clinical characterization and outcome. *Archives of Neurology* 1999;56:303–308. [PubMed: 10190820]
- Postman L, Alpern TG. Retroactive inhibition as a function of the time of interpolation of the inhibitor between learning and recall. *American Journal of Psychology* 1946;59:439–449.
- Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry* 1957;20:11–21.
- Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science* 2002;298:789–791. [PubMed: 12399581]
- Silverstein AB. Two-and four-subtest short forms of the Wechsler Adult Intelligence Scale-Revised. *Journal of Consulting and Clinical Psychology* 1982;50:415–418.
- Skaggs EB. Further studies in retroactive inhibition. *Psychological Monographs, Whole No* 1925;161:1–60.
- Skaggs EB. A discussion on the temporal point of interpolation and degree of retroactive inhibition. *The Journal of Comparative Psychology* 1933;16:411–414.
- Snodgrass JG, Vanderwart M. A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology. Human learning and memory* 1980;6:174–215. [PubMed: 7373248]
- Spear, NE.; Riccio, DC. *Memory: Phenomena and Principles*. Needham Heights, MA: Allyn & Bacon; 1994.
- Squire LR. Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learning & Memory* 2006;13:522–529. [PubMed: 17015849]

- Warrington EK, Weiskrantz L. Amnesic syndrome: Consolidation or retrieval? *Nature* 1970;288:628–630. [PubMed: 4990853]
- Warrington EK, Weiskrantz L. The effect of prior learning on subsequent retention in amnesic patients. *Neuropsychologia* 1974;12:419–428. [PubMed: 4437740]
- Warrington EK, Weiskrantz L. Further analysis of the prior learning effect in amnesic patients. *Neuropsychologia* 1978;16:169–177. [PubMed: 692841]
- Wechsler, D. Wechsler Adult Intelligence Scale-Revised. San Antonio: Psychological Corporation; 1981.
- Weiskrantz L. Comparative aspects of studies of amnesia. *Philosophical Transactions of the Royal Society of London* 1982;298:97–109. [PubMed: 6125979]
- Wixted JT. The Psychology and neuroscience of forgetting. *Annual Review of Psychology* 2004;55:235–269.

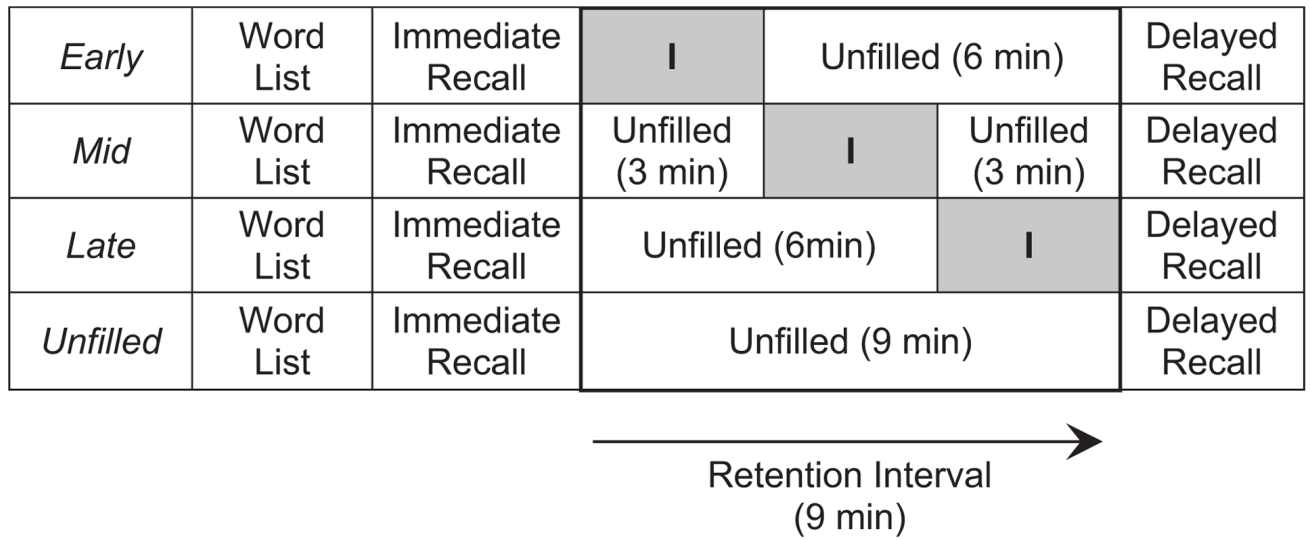


Figure 1.
 Experimental procedure: The Early, Mid, Late and Unfilled Conditions, I = Interference.

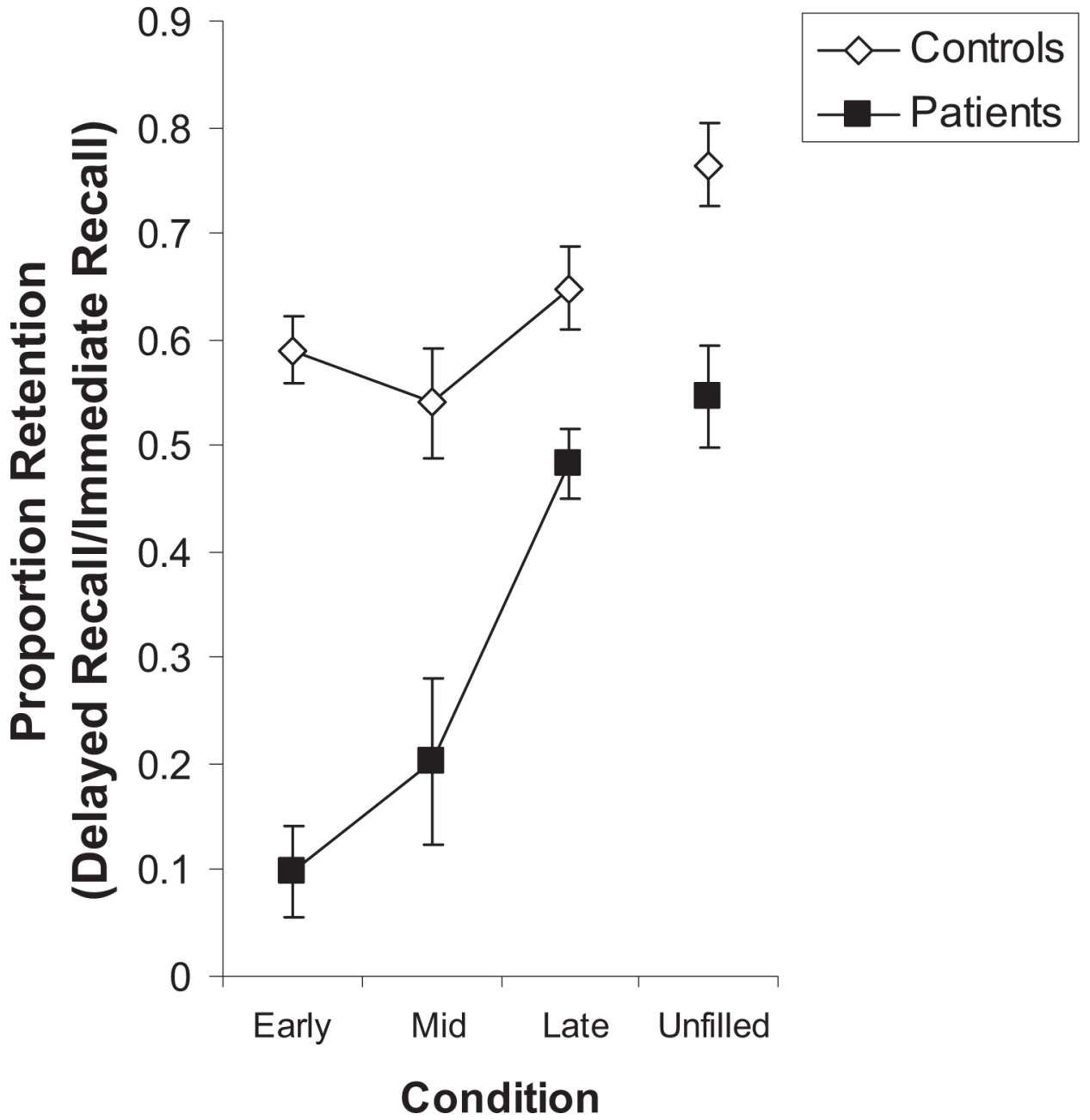


Figure 2. Mean proportion retention (delayed recall divided by immediate recall) as a function of group and condition. Error bars show the standard error of the mean (S.E.M.).

Table 1

Group Means and SDs for Selected Demographic and Neuropsychological Measures

	Patients (6f/6m)		Controls (11f/1m)	
	Mean	SD	Mean	SD
Age	73.75	(5.34)	70.33	(6.33)
WAIS-R Estimated IQ ¹	109.75	(9.73)	116.25	(7.03)
Mini Mental State Examination ^{2,o}	26.5	(1.83)	28.25	(1.29)*
Clinical Dementia Rating ³	0.5	(0)	0	(0)
Token Test (Language comprehension) ⁴	32.71	(1.7)	33.63	(1)
Verbal fluency (phonological) ⁵	8.42	(2.02)	9.92	(2.31)
Rey Figure Copy ⁶	31.88	(3.52)	34.08	(1.88)
Rey Figure Delayed Recall ⁶	11.79	(3.43)	17.25	(2.86)**
Word List Learning Total Immediate Recall ⁷	30.33	(4.38)	46.17	(5.44)**
Word List Delayed Recall ⁷	6.33	(1.37)	10.67	(1.23)**
Digit Span ⁸	5	(0.95)	5.64	(0.48)
Spatial Span (Corsi blocks) ⁹	4.25	(0.97)	4.75	(0.62)

Note. Group differences:

* $p < .05$.

** $p < .001$ (Digit span $p = .051$). All patients were diagnosed with amnesic Mild Cognitive Impairment (aMCI), the criteria being (a) a memory complaint corroborated by an informant, (b) objective memory impairment, (c) otherwise normal general cognitive function, (d) intact activities of daily living, and (e) an absence of dementia (Petersen et al., 1999). They all performed poorly on tests of LTM, yet within the normal range on tests of STM and other cognitive function. Moreover, they were not demented.

^o The significant group difference on the MMSE is due to significantly poorer memory performance (recall subscore) in the patients than the controls, $F(1, 23) = 8.49, p < .01$. The patients did not differ from the controls on any of the other subscores of the MMSE.

¹ Silverstein (1982);

² Folstein, Folstein, & McHugh (1975);

³ Hughes, Berg, Danziger, Coben, & Martin (1982);

⁴ De Renzi & Faglioni (1978);

⁵ Carlesimo, Caltagirone, & Gainotti (1996);

⁶ Osterrieth (1944);

⁷ Gonzales, Mungas, Reed, Marshall, & Haan (2001);

⁸ Wechsler (1981);

⁹ Milner (1971).

Table 2

Individual Immediate Recall Proportion (/15) Averaged Across the Four Conditions, and Individual Proportion Retention at Delayed Recall (Delayed/Immediate) in Each of the Four Conditions

Participant	Mean immediate recall proportion (/15)	Delayed retention (Delayed/Immediate)			
		Early	Mid	Late	Unfilled
Patient 1	0.28	0.20	0.00	0.50	0.75
Patient 2	0.17	0.00	0.00	0.70	0.50
Patient 3	0.32	0.00	0.00	0.40	0.40
Patient 4	0.27	0.00	0.00	0.70	0.40
Patient 5	0.33	0.00	0.00	0.40	0.40
Patient 6	0.30	0.00	0.40	0.30	0.67
Patient 7	0.27	0.00	0.80	0.60	0.67
Patient 8	0.30	0.25	0.60	0.50	0.60
Patient 9	0.33	0.40	0.00	0.50	0.33
Patient 10	0.38	0.00	0.30	0.30	0.83
Patient 11	0.32	0.00	0.00	0.40	0.60
Patient 12	0.35	0.33	0.30	0.50	0.40
Control 1	0.37	0.67	0.60	0.80	0.67
Control 2	0.42	0.57	0.60	0.70	0.86
Control 3	0.30	0.60	0.40	0.60	0.67
Control 4	0.38	0.50	0.20	0.50	0.57
Control 5	0.43	0.50	0.50	0.60	0.71
Control 6	0.38	0.33	0.40	0.40	0.60
Control 7	0.52	0.56	0.50	0.70	0.75
Control 8	0.38	0.67	0.80	0.70	1.00
Control 9	0.32	0.60	0.50	0.50	0.75
Control 10	0.37	0.67	0.80	0.80	0.80
Control 11	0.33	0.67	0.50	0.80	1.00
Control 12	0.37	0.75	0.70	0.70	0.80