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Wakeful rest benefits before and after encoding in anterograde amnesia

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Abstract

Objective: Studies have shown that patients with anterograde amnesia forget less episodic information after a delay if encoding is immediately followed by an unfilled period of wakeful rest. This benefit has been attributed to the reduced interference with the consolidation process. However, this account cannot directly explain improved retention in healthy adults resulting from pre-encoding rest. While benefits resulting from pre- and post-encoding rest can be alternatively explained via improved distinctiveness at retrieval, it has yet to be established whether both benefits are observable in amnesics. The aim of the current study was to assess whether amnesic patients showed improved retention of prose material after 10 minutes following both pre- and post-encoding unfilled intervals of wakeful rest.

Method: Twelve patients with anterograde amnesia were recruited. Participants completed four conditions. A short prose passage was aurally presented in each condition. Prose presentation was preceded and followed by a 9-minute delay interval. Delay intervals were either filled (spot-the-difference task) or unfilled (wakeful rest). Prose retention was assessed immediately after presentation and after 10 minutes.

Results: Prose retention was consistently better when wakeful rest followed prose encoding in comparison to a condition where an effortful task was encountered both before and after encoding.

Conclusions: Post-encoding wakeful rest alone substantially improves retention in amnesic patients. While pre-encoding wakeful rest elicits inconsistent benefits in amnesics, reduced retention following both pre- and post-encoding task engagement suggests that pre-encoding activity may still be relevant. Overall, our findings support consolidation interference explanations of forgetting in anterograde amnesia.

Keywords: Anterograde amnesia, retroactive interference, proactive interference, consolidation, temporal distinctiveness

Public significance statement: The present study reaffirms that patients with anterograde amnesia are able to retain more recently acquired episodic information if they rest briefly in a quiet, darkened room immediately after encoding. When encoding is instead followed by further sensory stimulation, retention of newly encoded prose material consistently declines.

These findings lend support towards theories suggesting that forgetting in anterograde amnesia occurs as a result of interference with consolidation.

Substantial forgetting of recently acquired episodic memories is frequently observed in patients with anterograde amnesia when memory acquisition is followed by a filled period of post-encoding activity, in which further sensory stimulation is encountered. Pronounced memory loss has been seen in patients with anterograde amnesia (Cowan, Beschin, & Della Sala, 2004; Dewar, Della Sala, Beschin, & Cowan, 2010) and those with amnesic mild cognitive impairment (aMCI; Della Sala, Cowan, Beschin, & Perini, 2005; Dewar, Garcia, Cowan, & Della Sala, 2009; Alber, Della Sala, & Dewar, 2014) and Alzheimer's disease (Dewar, Pesallaccia, Cowan, Provinciali, & Della Sala, 2012) even when encoding is succeeded by a relatively brief interval of post-encoding activity (10 minutes or less). However, patients with amnesia and impaired long-term memory (LTM) are often able to retain some episodic information if behavioural interference encountered immediately after encoding, or retroactive interference (RI; Müller & Pilzecker, 1900; see Dewar, Cowan, & Della Sala, 2007), is minimized momentarily via wakeful rest (Cowan et al., 2004; Della Sala et al.2005; Dewar et al, 2010, 2012; Alber et al., 2014). A temporary respite from sensory stimulation during an unfilled period consisting of wakeful rest in a quiet, darkened room has been shown to promote improved recall of episodic information. This benefit has been shown to be enduring, with improvements to LTM retention seen after several minutes following presentation (Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009, 2010, 2012) up to 7 days (Alber et al., 2014). Dewar and colleagues (2009) noted that even delaying sensory stimulation after encoding by 6 minutes can significantly improve retention in patients with impaired LTM. These studies overall demonstrate the initial fragility of newly acquired episodic memories in anterograde amnesia, but a preserved potential for stability under conditions of wakeful rest during a retention interval.

Such findings support consolidation interference accounts of forgetting which posit that post-encoding engagement with extraneous sensory stimuli profoundly disrupts the consolidation of newly encoded episodic memories in amnesics (Dewar et al., 2010; Dudai, 2004; Wixted, 2004). Consolidation is believed to be a fundamental process of memory involving the continuous post-encoding stabilization of memory traces into LTM (Wixted, 2004; Dudai, 2004). During the primary stage of synaptic consolidation that immediately follows encoding, initially-weak episodic memory traces are progressively strengthened (Dudai, 2004) via the automatic reactivation of traces during hippocampal replay (Carr, Jadhav, & Frank, 2011). Engagement in additional activity during this early post-encoding stage - mere minutes following memory acquisition - is believed to markedly impede LTM retention in amnesic patients by directly hindering early consolidation of the target memorandum. Post-encoding wakeful rest - in which exposure to sensory stimuli is vastly reduced - is assumed to promote the optimal conditions for uninterrupted consolidation that contribute to notable improvements in LTM retention seen across numerous studies (Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009; 2010; 2012; Alber et al., 2014). This benefit is not presumed to be a result of conscious subvocal rehearsal within preserved short-term memory (STM), given the length of delay intervals and the findings that some amnesic patients retained information even after sleeping through portions of the retention interval (Alber et al., 2014; Cowan et al., 2004; Dewar et al., 2010). Other findings supporting this suggestion that the benefit of wakeful rest in a quiet, dark room does not occur through STM maintenance are the impotence of RI or distractor tasks after a sufficient delay even though they would limit efforts to maintain the to-be-retained information within STM (Dewar et al., 2009, 2012; Alber et al., 2014), and the finding of wakeful rest benefits for the retention of presumably non-rehearsable non-word and non-verbal material (Dewar et al., 2014; Craig, Dewar, Harris, Della Sala, & Wolbers, 2015, 2016; Craig, Wolbers, Harris, Hauff, Della Sala, & Dewar, 2016).

While consolidation interference accounts provide a means of understanding how post-encoding activity may elicit pronounced forgetting in amnesics, they neglect the possible role of pre-encoding activity – or proactive interference (PI) - in forgetting among those with anterograde amnesia. Current consolidation interference accounts can only directly explain benefits to retention that result from unfilled periods of rest *after* new learning (Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009; 2010; 2012). Research has yet to thoroughly explore whether an unfilled interval *preceding* new learning could lead to similar benefits in amnesic patients. Past studies had reported that PI can negatively impact later recall in amnesic patients (Warrington & Weiskrantz, 1970, 1974). These findings were later brought into question following failed replications (Warrington & Weiskrantz, 1978). However, recent studies have demonstrated improved retention following longer pre-encoding periods of low mental activity among samples of healthy adults (Ecker, Tay, & Brown, 2015a; Ecker, Brown, & Lewandowsky, 2015b). In these studies, healthy adults performed poorer on tests of delayed free-recall if the encoding of a list of unrelated words had come moments before the encoding of the target list (between 15 to 60s). However, if the encoding of a previous list occurred 120s to 240s prior to target list encoding, then retention of the target material was significantly improved in comparison. These findings have been accounted for in terms of the temporal distinctiveness hypothesis (Brown, Neath, & Chater, 2007). It is unknown whether these benefits may extend to patients with anterograde amnesia. If so, it is possible that an alternative account may provide a more encompassing explanation of forgetting seen in patients presenting with anterograde amnesia.

Temporal interference accounts of forgetting - more specifically, those involving temporal distinctiveness (Brown et al., 2007) - would predict both pre- and post-encoding interference effects. This kind of account is based on the assumption that items within memory are positioned on a temporal dimension that is utilised in guiding retrieval. A determining factor of retrieval success is the distinctiveness of a given memory on this temporal dimension. Distinctiveness itself is determined by the relative temporal proximity of memories with respect to one another, which increases as the interval between initial learning and later retrieval lengthens (Brown et al., 2007; Brown, Preece, & Hulme, 2000; Neath, 1993). A particular memory may be more indistinct, hence harder to retrieve later if memory acquisition is immediately preceded and/or followed by further memories. What is relevant is that this account can simultaneously explain the benefits observed following longer pre- and post-encoding periods of low mental activity in healthy adults (Ecker et al., 2015a) and also the benefits observed under conditions of minimal RI discussed previously. This is based on the absence of neighbouring pre- and post-encoding memories reducing the distinctiveness of the target memorandum at later recall.

There are a few caveats to this account. The research specifically validating temporal interference accounts utilises brief delay intervals (from seconds to four minutes; Ecker et al., 2015a, 2015b), which are substantially shorter than the intervals typically employed in patient studies of minimal RI (ranging between 10 minutes and 7 days; Dewar et al., 2010, Alber et al., 2014). A key principle of temporal interference accounts presumes that short and long-term memory are not distinct (Brown et al., 2007). As such, it follows that benefits of temporal isolation seen over short delays could scale up to the longer intervals seen in other studies. However, the scaling of temporal isolation effects has not been investigated over retention periods lasting longer than 4 minutes (Ecker et al., 2015a, 2015b). It thus remains unknown whether such scaling can be seen across extended intervals matching past minimal

RI research (i.e., 10 minutes; Dewar et al., 2009, 2010). Additionally, investigations of temporal isolation effects have only been conducted across samples of healthy adults. Following this, it has yet to be established whether similar effects can also be observed in patients with anterograde amnesia. Given that these studies of healthy adults utilised rest periods consisting of low mental activity (i.e., tone-detection task), observations of similar benefits of temporal isolation would be unlikely across patient samples. This argument can be made based on past research that has demonstrated increased forgetting in amnesic patients following post-encoding engagement in a similar tone-detection task (Dewar et al., 2010). Therefore it seems plausible that such activity does not minimize interfering stimulation to the same degree as wakeful rest in an environment void of incoming sensory stimulation (Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011; Wixted, 2004; Dewar et al., 2009). On the basis that amnesic patients have a heightened vulnerability to interference, low mental activity during rest periods may not allow for a restful state to be achieved in comparison to healthy samples.

In consideration of the points above, the aim of the current study was to assess whether patients with anterograde amnesia were able to retain newly encoded episodic information (i.e., prose passages) if the delay intervals preceding and/or following encoding were filled (i.e., spot-the-difference task) or unfilled (i.e., wakeful rest). Our aim was chosen as a means of establishing whether interference with consolidation or temporal interference provided a more appropriate account of forgetting in anterograde amnesia. We assessed retention after 10 minutes following the manipulation of 9-minute pre- and post-encoding delay intervals to see whether observed benefits made in previous research on healthy adults (Ecker et al., 2015a, 2015b) could be replicated in a sample of amnesic patients over an extended retention period.

Consolidation interference accounts would predict maximal LTM retention within conditions in which RI is minimized via unfilled post-encoding delay intervals. This is based on the notion that the consolidation of the prose material would remain uninterrupted if wakeful rest was encountered immediately after encoding (Dudai, 2004; Wixted, 2004). Conversely, LTM retention would be expected to be substantially poorer within conditions where RI is present following filled post-encoding intervals. During such conditions, consolidation would be disrupted following post-encoding engagement in further sensory stimulation (i.e., spot-the-difference task). There would be no reason to expect an effect of minimising PI before encoding of the stimuli to be remembered. In contrast, from the perspective of temporal interference accounts, LTM retention would be expected to be substantially better under a condition in which both RI and PI have been minimized following unfilled pre- and post-encoding delay intervals. This is due to the bi-directional temporal isolation of the prose material within this condition leading to the pronounced distinctiveness of this material at later retrieval. Under conditions where the prose material is temporal isolated in only one direction (i.e., following either an unfilled pre- or post-encoding delay interval), retention would be intermediate between the condition with no RI or PI and the condition with both. Retention under a condition where both intervals are filled is would be expected to be vastly impaired due to the absence of any temporal isolation. Under this condition, prose material would be expected to be indistinct at retrieval, resulting in observations of markedly poor delayed free-recall.

Methods

Participants

Twelve patients with a diagnosis of anterograde amnesia (7m/5f, mean age = 53.75 years, age range = 22 – 82 years; mean education = 11.58 years, education range = 5 – 17 years) entered the experiment (see Table A1 and Table A2 for demographic and anatomical measures of each amnesic patient). All participants were recruited and tested at the Dipartimento di Riabilitazione, Ospedale Somma Lombardo, Italy. All participants were native-Italian outpatients with no known pre-morbid psychiatric or neurological histories. All participants were assessed over numerous neuropsychological tests (see Table B1 and Table B2 for neuropsychological measures of each amnesic patient) that were conducted during a separate session prior to experimental testing. Performances across these tests were used in conjunction with inclusion criteria to identify participants who were appropriate for the current experiment. The inclusion criteria, which closely matched that used in similar past research (Cowan et al., 2004; Dewar et al., 2010), consisted of the following: (a) memory problems supported by self-reports and reports provided by caregivers on the Prospective and Retrospective Memory Questionnaire (PRMQ; Smith, Della Sala, Logie, & Maylor, 2000); (b) classification as amnesic based on the Rivermead Behavioural Memory Test (RBMT-3; Wilson et al., 2008); (c) performance below cut-off for normality in verbal delayed recall (Rey's 15 words; Carlesimo et al., 1996) and nonverbal delayed recall (Rey Figure Copy; Caffarra, Vezzadini, Deici, Zonato, & Venneri, 2002); (d) normal performance in verbal and nonverbal short term memory tasks (digit span and Corsi blocks; Orsini et al., 1987); (e) score within the normal range on test of verbal comprehension (Token Test; De Renzi & Faglioni, 1978); (f) score within the normal range on an aphasia test battery including comprehension (Aachen Aphasie Test; De Bleser et al., 1986); (g) score within the normal range on test of verbal fluency (Novelli et al., 1986); (h) scores within the normal range in verbal reasoning (Verbal Judgement Test; Spinnler & Tognoni, 1987); (i) scores within the normal range in nonverbal reasoning (Raven's Progressive Matrices; Basso, Capitani, & Laiacona, 1987); (j) scores within the normal range on the Mini Mental State Examination (MMSE; Measso et al., 1993).

Materials and Procedure

Figure 1 illustrates the procedure of the experiment. Participants took part in four conditions. Each condition either involved (a) an unfilled pre-encoding delay interval consisting of wakeful rest and an unfilled post-encoding delay interval consisting of wakeful rest – labelled UU condition; (b) a filled pre-encoding delay interval consisting of a spot-the-difference task and a filled post-encoding delay interval consisting of a spot-the-difference task – labelled FF condition; (c) an unfilled pre-encoding delay interval consisting of wakeful rest but a filled post-encoding delay interval consisting of a spot-the-difference task – labelled UF condition; (d) a filled pre-encoding delay interval consisting of a spot-the-difference task but an unfilled post-encoding delay interval consisting of wakeful rest – labelled FU condition. Conditions were spread across two separate testing sessions, each consisting of two conditions. Separate testing sessions were employed to alleviate potential fatigue effects seen in similar studies (Ecker et al., 2015a). The second testing session took place between 1-7 days after the first testing session. Performances across conditions within the second testing session did not differ significantly depending on its temporal proximity with the first testing session.

Presentation of a prose passage occurred after each 9-minute pre-encoding delay interval within all four conditions. The four prose passages used in the current study were taken from the Italian variant of the Rivermead Behavioural Memory Test (RBMT-3; Beschin, Urbano, & Treccani, 2013). Each prose passage consisted of 21 story "ideas". Prose passages were presented verbally to the participants, with a test of immediate free-recall following directly after. During immediate free-recall, participants were instructed to attempt to recall the prose passage verbatim. Delayed free-recall of each prose passage was also assessed. Each test (four in total, one test for each prose passage) took place immediately following the short distractor task within each condition. Individual tests for each story were chosen instead of a singular assessment of all presented stories to ensure that the temporal distance between prose presentation and delayed free-recall was consistent across all conditions. If multiple prose passages had been assessed within a single test, it could have favoured the more recently acquired prose passage.

Prose Passage Scoring

Only story ideas that were recalled verbatim were scored as correct within the current experiment. Story ideas which were partially recalled (i.e., use of approximations, omissions of minor details or subtle errors) were given half-marks. Scoring took place after testing using audio recordings of free-recall. Initial scoring was checked against the scoring of a second rater who was blind to the intentions of the experiment. Inter-rater reliability (IRR) was computed using two-way random, consistency, average-measures intraclass correlations coefficient (ICC: McGraw & Wong, 1996). Mean ICC across immediate and delayed free-recall scores was in the excellent range for both groups (ICC = .764 for immediate, ICC = .798 for delayed; Cicchetti, 1994; Hallgren, 2012). These findings represent a high degree of agreement between the two raters. The original scores were subsequently used in later analyses. Reported findings did not vary significantly depending on which set of scores were used.

A measure of proportion retention for the prose passages within each condition was calculated by dividing the number of story ideas recalled correctly after delayed free-recall by the number of story ideas recalled correctly at immediate free-recall.

Delay Intervals

Across the four conditions, we manipulated whether the 9-minute pre-encoding and post-encoding delay intervals immediately preceding and following prose presentation and immediate free-recall assessment would be filled or unfilled.

Filled delay intervals consisted of a mentally effortful spot-the-difference task. Within the spot-the-difference task, participants were visually presented with picture pairs sequentially on a computer screen for 25 seconds each. Participants were tasked with identifying two subtle differences between each pair of pictures during this time. Following this, a 5 second feedback phase occurred in which the differences were highlighted on-screen. The feedback phase was included to maintain consistent participant engagement in the task and reduce task-irrelevant thinking (Varma et al., 2017). Participants were required to identify the subtle differences by pointing them out to the experimenter without talking to ensure the task did not entail oral components matching prose recall. The pictures – photographs of complex real-world scenes (e.g., landscapes, animals and people) – were not directly related semantically to the prose passage material. Before the experiment, participants completed a practice trial consisting of 2 picture pairs in order to establish familiarity with the task. Future trials faced during the delay intervals consisted of 18 picture pairs and took 9 minutes to complete. The spot-the-difference task was also used as a distractor task within the current experiment. A short distractor task was employed prior to delayed free-recall within each condition to ensure that any conscious subvocal rehearsal occurring during post-encoding wakeful rest would be interrupted. The interruption of any rehearsal strategies prior to delayed free-recall was presumed to result in the extinguishing of information being maintained within STM. Further measures to mitigate rehearsal effects are discussed later. The distractor task consisted of 2 picture pairs and lasted for 1 minute. Overall performance of participants within each trial was scored based on the total number of correctly identified differences divided by the total number of differences (36 differences within each condition trial, 4 differences within each distractor trial).

Unfilled delay intervals consisted of wakeful rest. During unfilled delay intervals, participants were instructed to rest quietly in the testing room. During this time, lights were turned off to reduce any further sensory stimulation. The unfilled delay interval commenced as soon as the experimenter exited the room. The experimenter returned once 9 minutes had elapsed. Participants were instructed to relax during the unfilled delay intervals, feeling free to think about anything that came to mind. Participants were advised against any activity involving external stimuli (e.g., the use of mobile phones).

Measures To Reduce and Account for Possible Rehearsal Effects

Participants were not initially informed about the intentions of the study (i.e., memory) to avoid the anticipation of tests of delayed free-recall and to reduce attempts to maintain prose material in STM. Participants were made to believe that the assessment of delayed free-recall within the first condition was conducted solely to address a technical issue with the recording that had occurred during the first immediate test. The test of delayed free-recall within the second condition was assumed to come as another surprise to participants since delayed free-recall within the first condition was seen as a one-time occurrence.

In addition to hiding the intentions of the experiment for the purpose of reducing anticipated tests and resultant rehearsal attempts, counterbalancing measures were used to ensure any potential benefits resulting from active rehearsal could be accounted for. All participants were quasi-randomly allocated to one of the two following condition order groups prior to the commencement of the experiment: (a) FU, UU, UF, FF, (b) UF, UU, FU, FF. The two counterbalanced condition orders were formed to ensure that surprise delayed free-recall would be experienced across half of our sample during the FU and UF conditions. By comparing surprise vs expected delayed free-recall across the FU and UF conditions, we could directly see whether our distractor tasks were sufficient at extinguishing STM maintenance.

At the end of each session, participants were asked to complete a short questionnaire. The main purpose of the questionnaires was to gain a more accurate account of whether or not conscious subvocal rehearsal occurred during the experiment; and under what conditions. Questionnaires were completed by hand.

Statistical Analysis

All statistical analyses were conducted using JASP (JASP Team, 2018) as a means of conducting Bayesian analyses alongside conventional analyses. From the conventional analyses, we derive t values and effect size d for descriptive purposes; whereas a Bayesian analysis yields the probability that the data came from a null hypothesis as opposed to a reasonable collection of possible non-nulls. Bayes Factors of 3 or above are taken as moderate evidence favouring the non-null. Bayes Factors below 3 are taken as anecdotal evidence favouring the non-null, and is more in support of the null (van Doorn et al., 2019). We compared immediate free-recall across conditions via Bayesian paired-samples t-tests. We also conducted Bayesian paired-samples t-tests of proportion retention across all conditions (FU vs UF vs UU vs FF). Additional Bayesian analyses were conducted to see whether there were potential order effects or differences in performance based on self-reported conscious subvocal rehearsal or expectance of delayed free recall.

Results

Immediate Free-Recall

Table C shows mean immediate free-recall performance of amnesic patients (n = 12) across all conditions. Conventional and Bayesian paired-samples t-tests demonstrated no strong evidence that immediate free-recall performance was notable different across all conditions ($p > .05$, $BF_{10} < 1.5$). Additionally, a conventional and Bayesian one-way analysis of variance (ANOVA) found no firm evidence supporting meaningful differences in mean immediate free-recall depending on whether the pre-encoding delay interval was filled or unfilled ($p > .05$, $BF_{10} = .355$).

The use of proportion retention allows us to mitigate individual differences in immediate free-recall that may possibly result from variabilities in cognitive deficits extending beyond memory.

Proportion Retention

Figure 2 demonstrates the mean proportion retention of the prose material across all conditions in the delayed test compared to the immediate test. Conventional and Bayesian paired-samples t-tests were conducted to analyse whether there were significant differences in proportion retention between each condition. Proportion retention was significantly lower in the FF condition when compared to both the UU and FU condition, UU vs FF: $t(11) = 2.252$, $p = .023$, $d = .650$, $BF_{10} = 3.440$; FU vs FF: $t(11) = 3.060$, $p = .011$, $d = .883$, $BF_{10} = 5.539$. It should be noted that one of the t-tests were performed with the adoption of a one-tailed hypothesis (i.e., UU vs FF). This was done with respect to the shared predictions of the two accounts (discussed previously) which would expect to see superior performance within the UU condition in comparison to the FF condition. There was only anecdotal evidence to suggest notable differences among the other conditions, UU vs FU: $t(11) = -.041$, $p = .968$, $d = -.012$, $BF_{10} = .288$; UU vs UF: $t(11) = -.213$, $p = .835$, $d = -.061$, $BF_{10} = .293$; FU vs UF: $t(11) = -.193$, $p = .851$, $d = -.056$, $BF_{10} = .292$; UF vs FF: $t(11) = 1.860$, $p = .090$, $d = .537$, $BF_{10} = 1.068$. These findings confirm the importance of post-encoding wakeful rest, though it is noteworthy that in the presence of post-encoding task engagement, the effects of pre-encoding wakeful rest were indeterminate.

Possible Effects of Order and Active Rehearsal

Based on self-reports from the post-experimental questionnaires, seven out of twelve participants did not expect delayed free recall during the first testing session (i.e., during the first two conditions of the experiment). Among the five participants who expected a delayed test, only two expected assessments of delayed free recall across both conditions. The remaining three participants only expected a test during the second condition of the first testing session. Bayesian independent-samples t-tests indicated no strong evidence supporting differences on the FU and UF condition based on condition order, whether participants expected delayed free recall during the first condition or not, and whether participants reported to have attempted intentional rehearsal ($p > .05$, $BF_{10} < 1$). In addition to this, there was not a notable difference in proportion retention among participants who reported to have rehearsed vs those who did not within the UU condition ($p > .05$, $BF_{10} < 1$), or whether they expected a test of delayed recall during this condition ($p > 0.05$, $BF_{10} < 1$). From this, it can be concluded that the distractor task was sufficient in extinguishing STM and preventing superior memory retention via conscious subvocal rehearsal.

Spot-the-difference Task Performance

Conventional and Bayesian paired-samples t-tests established a learning effect whereby amnesic patients scored better on the spot-the-difference tasks occurring during the pre- and post-encoding delay interval within the final condition (i.e., the FF condition) when compared to the first condition (either the FU or UF condition), pre-encoding: $t(1, 11) = 2.851$, $p = .016$, $d = .823$, $BF_{10} = 4.096$; post-encoding: $t(1, 11) = 3.422$, $p = .006$, $d = .988$, $BF_{10} = 9.359$. This was also seen when compared to the third condition spot-the-difference task (either the FU or UF condition), pre-encoding: $t(1, 11) = 2.190$, $p = .051$, $d = .632$, $BF_{10} = 1.635$; post-encoding: $t(1, 11) = 2.233$, $p = .047$, $d = .645$, $BF_{10} = 1.730$. However, the results from the Bayesian analyses show a reduction in support for notable differences in task performance.

This was also seen in performance on the 1-minute spot-the-difference tasks prior to delayed free recall in each condition, where amnesic patients scored better on the last condition compared to the first two conditions. This may be indicative of growing familiarity with the demands of the task.

Multiple Pearson correlations demonstrated no significant associations between spot-the-difference task performance and proportion retention across all conditions consisting of interpolated tasks ($p > .05$). An absence of significant negative correlations between interpolated task performance and later memory performance supports the notion that no trade-offs occurred between these tasks. In other words, it appears that participants did not disengage in the spot-the-difference tasks in order to maintain prose material in STM via rehearsal strategies.

Discussion

Patients with anterograde amnesia were better able to retain substantial portions of newly encoded prose material after a delay of 10 minutes when an unfilled period consisting of wakeful rest immediately followed prose learning (i.e., during the UU and FU condition). This generally supports the notion that individuals with anterograde amnesia maintain a poor but nevertheless functional ability to commit new episodic content to LTM; an ability that is profoundly promoted by minimal RI via post-encoding wakeful rest (Cowan et al., 2004; Della Sala et al., 2005; Dewar et al., 2009; 2010; 2012; Alber et al., 2014). This benefit does not appear to be a product of uninterrupted STM maintenance in the present study since short distractor tasks preceding delayed free-recall adequately extinguished any information maintained in STM in those who engaged in conscious subvocal rehearsal during post-encoding wakeful rest.

While improved retention following the minimization of post-encoding activity was persistently observed among amnesic patients within the current study, the observation of benefits following the reduction of pre-encoding activity was less consistent. Prose retention was equally improved in amnesic patients within the current study as a result of post-encoding wakeful rest, regardless of whether the pre-encoding delay interval was filled or unfilled (i.e., during the FU and UU conditions respectively). This can be seen when the mean proportion of prose items retained across these conditions is compared with that achieved across the condition in which both pre- and post-encoding mental exertion is experienced (i.e., during the FF condition). However, the increase in mean proportion retention following the individual introduction of pre-encoding wakeful rest within the UF condition was not shown to be statistically notable when contrasted with the FF condition. It should be highlighted that mean performance across the UF condition was numerically comparable with that seen across the UU and FU conditions (see Figure 2). However, the variability of performances within this condition was substantial. This variance indicates that some, but not all, amnesics might have been able to benefit solely from pre-encoding wakeful rest. However, it remains unclear from the current data whether the ability to benefit from the reduction of pre-encoding activity is associated with a particular lesion site.

The absence of improved retention following pre-encoding wakeful rest was also seen when the current paradigm was conducted across a sample of healthy adults matched for age, sex, and years of education to the patient group (see Supplementary material for healthy control data and analyses). This may indicate that, irrespective of cognitive ability, pre-encoding activity alone does not have a considerable impact on retention when assessed over extended periods. This stands against research which has demonstrated improved retention in healthy adults over a shorter retention period (i.e., 2-4 minutes; Ecker et al., 2015a; 2015b) when new learning was preceded by longer pre-encoding periods of low mental activity.

While it may be concluded that pre-encoding activity is largely irrelevant when reflecting on forgetting among the majority of amnesic patients, this is potentially deceptive. The poorest mean proportion retention was observed across amnesic patients on the FF condition following the concurrent presence of both pre- and post-encoding activity. Among amnesics, the encountering of both RI and PI within a single condition (i.e., the FF condition) imposes a greater detriment to retention when compared to the impacts of RI or PI alone (seen across the UF and FU conditions). This unique observation may indicate that RI and PI may play an interactive role when simultaneously imposed on a single item (or in the instance of the current study, a prose passage). However, the nature of this relationship is still not clearly understood and warrants further exploration.

Overall, the findings from the current study favour consolidation interference accounts based on the greater importance of post-encoding activity as a determinant of successful retention and retrieval. When post-encoding interference is encountered (i.e., during the UF and FF conditions), the consolidation of the prose material is believed to be interrupted via the processing of additional material within the spot-the-difference task. This is directly in line with previous research which has demonstrated improvements to LTM retention following minimal RI (Cowan et al, 2004; Della Sala et al., 2005; Dewar et al., 2009, 2012; Alber et al., 2012). Additionally, it supports the notion that forgetting can be elicited via the post-encoding introduction of stimuli which is modally and semantically unrelated to the to-be-retained material (Dewar et al., 2010).

Such findings have been partially attributed to resource competition (Wixted, 2004; Dewar et al., 2009). It is assumed that all cognitive processes - including the encoding and consolidation of episodic information (Varma et al., 2017) – require an amount of resources drawn from a finite “energy budget” in order to be performed (Raichle & Gusnard, 2002;

Wixted, 2004). This limited cognitive resource, which is distributed among many cognitive processes (Raichle & Gusnard, 2002) is believed to be substantially constrained in those with impaired LTM (Wixted, 2004; Dewar et al., 2009), although this is yet to be fully understood. Given this assumption, the reallocation of resources following the processing of post-encoding stimuli (i.e., during the spot-the-difference task) may have resulted in the depletion of resources available for the consolidation of previously acquired episodic information (i.e., prose material). As a result, synaptic consolidation is believed to be greatly hindered and episodic memory traces remain in a weakened state that leaves them prone to forgetting. Conversely, under conditions of minimal post-encoding sensory stimulation (i.e., during the UU and FU conditions), the consolidation of previously learned episodic memories can remain uninterrupted in amnesic patients as the significant division of residual resources is avoided.

While the sole benefit of post-encoding wakeful rest could also be seen as supportive evidence for temporal interference accounts, the inconsistent nature of benefits observed following pre-encoding wakeful rest – in which uni-directional temporal isolation is also attained - weakens this position. As such, marked benefits from uni-directional temporal isolation were only observed in amnesic patients when it occurred after encoding, but not before. This stands in contrast to studies conducted on healthy samples which saw benefits following both pre- and post-encoding rest benefits over shorter intervals (Ecker et al., 2015a). Given this discrepancy, the current results may indicate that temporal interference accounts exclusively explain forgetting in healthy populations, or forgetting across briefer windows of time.

One concern surfacing from the current study, which may explain the lack of specific support for temporal interference accounts, relates to the interference task utilized within the study. It could be argued that tasks may elicit differential interfering effects based on a number of interlacing factors. Such factors may include the temporal location of the task (i.e., before or after new learning) and the semantic relatedness of the interfering material within the task to the to-be-retained material. RI can be elicited via the introduction of post-encoding tasks which are semantically and modally dissimilar in nature to the to-be-retained information (see Dewar et al., 2010). As such, RI can be evoked without the need for retrieval competition. However, given that past research investigating PI effects have typically utilised similar material (Underwood, 1957; Warrington & Weiskrantz, 1970, 1974; see Wixted, 2004 for review), an observable effect of PI may be conditional based on the presence of material similarity and competition at retrieval. If this is the case, it may be unsurprising that clearer effects of RI and a reduced negative impact of PI were observed within our study due to the use of a distinct interference task (i.e., visual spot-the-difference task). However, considering that PI effects have been observed following the reduction of shared cues (Warrington & Weiskrantz, 1978), and in some cases not observed when target material had many associative connections to previously learned information (Underwood & Postman, 1960), material similarity may not be a necessity for PI to occur.

The poor immediate free-recall performance of the amnesic patient sample may also be a concern within the current study. The amount of material initially encoded was substantially small, which may have contributed to an increased difficulty in establishing more notable differences between certain key conditions – mainly, between the FU and UF conditions. However, poor immediate free-recall for prose material (Cowan et al., 2004; Dewar et al., 2010; Alber et al., 2014), as well as for word lists (Dewar et al., 2012), is a common observation in amnesic patients. A LTM component is likely present within our assessment of immediate free-recall, leading to likely observations of poorer performances as a result of the limited LTM capacities of this group. Poor immediate free-recall performance within our current sample may be indicative of a patient sample that is severely impaired. This can also be considered in conjunction with the variability of performances seen across our patients, with some patients performing at floor regardless of whether unfilled intervals of wakeful rest preceded or followed prose presentation. While it was not evident from our sample that floor performances corresponded to specific aetiologies, future research adopting the current paradigm could investigate this further; assessing and comparing performance across a larger number of patients who vary based on lesion loci (i.e., frontal vs temporal patients).

In conclusion, patients with anterograde amnesia appear to be predominantly susceptible to interference resulting from post-encoding engagement with further sensory stimulation. Reducing post-encoding activity via wakeful rest appears to facilitate the successful retention of newly encoded episodic information in amnesics that would have otherwise been forgotten over a period of 10 minutes. Given that the minimization of pre-encoding activity at most may have led only to selective improvements to the retention of episodic memory in amnesics over this time period, accounts expecting notable benefits remain unsupported by the current findings. Rather, explanations which emphasize the importance of post-encoding effects – such as the consolidation interference account – seem to better fit the pattern of forgetting seen among amnesics within the current study. However, the novel observation of increased forgetting following the simultaneous presence of PI and RI alludes to a smaller role of PI that could be explored across amnesic samples that share common lesion sites (i.e., patients with temporal, frontal lobe damage).

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Table A1

Selected demographic and anatomical measures for each amnesic patient (P1-P6)

Measure	Amnesic patients (P1 – P6)					
	P1	P2	P3	P4	P5	P6
Age	82	54	22	52	55	57
Education (years)	10	13	11	8	17	13
Gender	m	m	f	f	m	m
Aetiology	CPCI	HYP	TBI	ISCH	OH	A
Known lesion sites	LRF	LRF	DAI, LFT	RTP	BA	LRF, RMT
Days since damage	170	95	1145	100	1330	900

Note. A = aneurysm, CPCI = chronic progressive cognitive impairment, HYP = hypoxia, ISCH = ischemia, OH = obstructive hydrocephalus, TBI = traumatic brain injury, L = left; R = right; F = frontal; P = parietal; T = temporal, M = medial, DAI = diffuse axonal injury, BA = territory of the basilar artery, according to CT or MRI.

Table A2

Selected demographic and anatomical measures for each amnesic patient (P7-P12)

Measure	Amnesic patients (P7 – P12)					
	P7	P8	P9	P10	P11	P12
Age	58	32	72	42	52	67
Education (years)	8	13	5	13	13	15
Gender	f	m	m	m	f	f
Aetiology	A	TBI	S	TBI	PI	H
Known lesion sites	DAI, LRF	LRF, LT	CR	RF	PR	BA
Days since damage	1275	950	105	1095	190	2190

Note. A = aneurysm, H = haemorrhage, PI = pontine ischemia, S = stroke, TBI = traumatic brain injury. L = left; R = right; F = frontal; T = temporal, DAI = diffuse axonal injury, BA = territory of the basilar artery, PR = pons region, CR = corona radiate, according to CT or MRI.

Table B1

Selected neuropsychological measures for each amnesic patient (P1-P6)

Measure	Amnesic patients (P1-P6)						Criteria
	P1	P2	P3	P4	P5	P6	
PRMQ Patient[a]	37	42	27	28	25	34	> 0
PRMQ Caregiver[a]	47	69	38	36	63	62	> 0
RBMT-3 classification[b]	Sig	Sig	Sig	Bor*	Sig	Sig	Sig impair
Rey's 15 words - delayed[c]	2	0	1	3	4	1	< 4.6
Rey figure copy[d]	31	33	34	30	36	36	> 28.87
Rey figure delayed[d]	1	5	10.5*	13*	5.5	7.5	< 9.46
Digit span[e]	4	5	5	7	5	4*	> 3.5
Corsi blocks[e]	4	4	4	4	4	4	> 3.25
Token test[f]	29	34	32	34	36	32	> 26.2
AAT[g]	NA	NA	NA	NA	NA	NA	NA
Phonological fluency[h]	20	34	35	18	32	17*	> 17.35
Verbal reasoning[i]	47	39	52	46	47	54	> 32
Raven progressive matrices[j]	18	23	35	17*	36	31	> 18
MMSE[k]	24	26	26	28	30	24	> 24

Note. PRMQ = Prospective and Retrospective Memory Questionnaire, RBMT-3 = Rivermead Behavioural Memory Test-3, AAT =Aachen Aphasia Test, MMSE = Mini-mental state examination, Sig = significant impairment, Bor = borderline impairment, NA = no aphasia, * does not match inclusion criteria.

[a] Smith, Della Sala, Logie, & Maylor, 2000, [b] Wilson et al., 2008, [c] Carlesimo et al., 1996, [d] Caffarra et al., 2002, [e] Orsini et al., 1987, [f] De Renzi & Faglioni, 1978, [g] De Blesser et al, 1986, [h] Novelli et al., 1986, [i] Spinnler & Tognoni, 1987, [j] Basso et al., 1987, [k] Della Sala et al., 2003, [l] Laiacona et al., 2000, [k] Measso et al., 1993.

Table B2

Selected neuropsychological measures for each amnesic patient (P7-P12)

Measure	Amnesic patients (P7-P12)						Criteria
	P7	P8	P9	P10	P11	P12	
PRMQ Patient[a]	33	21	30	47	51	39	> 0
PRMQ Caregiver[a]	57	35	39	38	67	47	> 0
RBMT-3 classification[b]	Sig	Sig	Av*	Sig	Sig	Sig	Sig impair
Rey's 15 words – delayed[c]	1	3	2	4	3	3	< 4.6
Rey figure copy[d]	36	31	7.5*	36	18.5*	33	> 28.87
Rey figure delayed[d]	6	15*	4.5	10*	7	6	< 9.46
Digit span[e]	5	5	4	6	6	5	> 3.5
Corsi blocks[e]	4	3*	5	7	5	6	> 3.25
Token test[f]	33	33	29	34	34	33	> 26.2
AAT[g]	NA	NA	NA	NA	NA	NA	NA
Phonological fluency[h]	16*	34	23	42	30	15*	> 17.35
Verbal reasoning[i]	47	44	33	53	38	45	> 32
Raven progressive matrices[j]	22	34	18	36	32	35	> 18
MMSE[k]	25	21*	24	29	25	28	> 24

Note. PRMQ = Prospective and Retrospective Memory Questionnaire, RBMT-3 = Rivermead Behavioural Memory Test-3, AAT =Aachen Aphasia Test, MMSE = Mini-mental state examination, Sig = significant impairment, Av = average performance, NA = no aphasia, * does not match inclusion criteria.

[a] Smith, Della Sala, Logie, & Maylor, 2000, [b] Wilson et al., 2008, [c] Carlesimo et al., 1996, [d] Caffarra et al., 2002, [e] Orsini et al., 1987, [f] De Renzi & Faglioni, 1978, [g] De Blesser et al, 1986, [h] Novelli et al., 1986, [i] Spinnler & Tognoni, 1987, [j] Basso et al., 1987, , [k] Measso et al., 1993.

Table C

Mean immediate free-recall performance across all experimental conditions

Condition	Mean	SD	SEM
UU	.264	.095	.028
FU	.194	.094	.027
UF	.200	.096	.028
FF	.230	.089	.026

Note. UU = unfilled pre-encoding delay interval – unfilled post-encoding delay interval; FU = filled pre-encoding delay interval – unfilled post-encoding delay interval; UF = unfilled pre-encoding delay interval – filled post-encoding delay interval; FF = filled pre-encoding delay interval – filled post-encoding delay interval, SD = Standard deviation, SEM = Standard error of the mean.

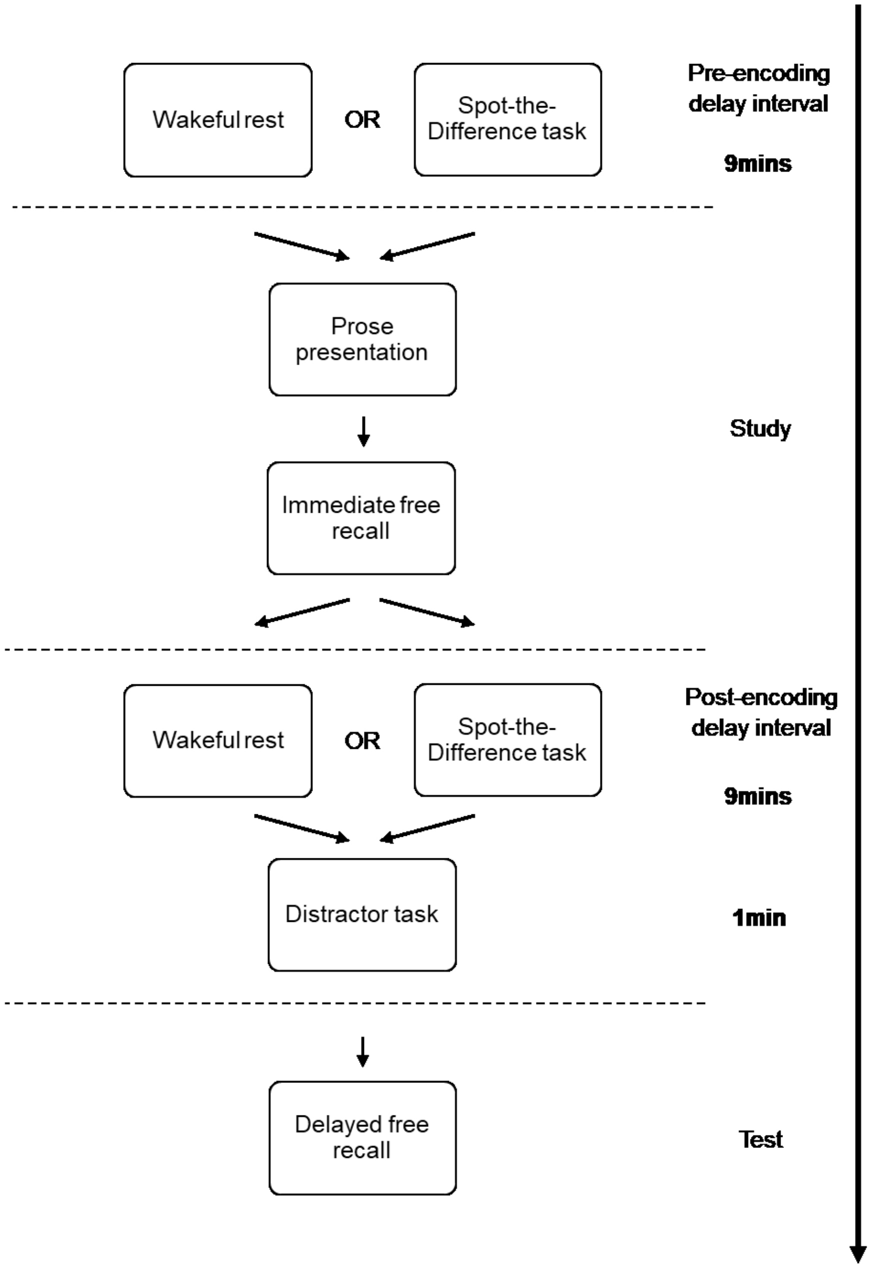
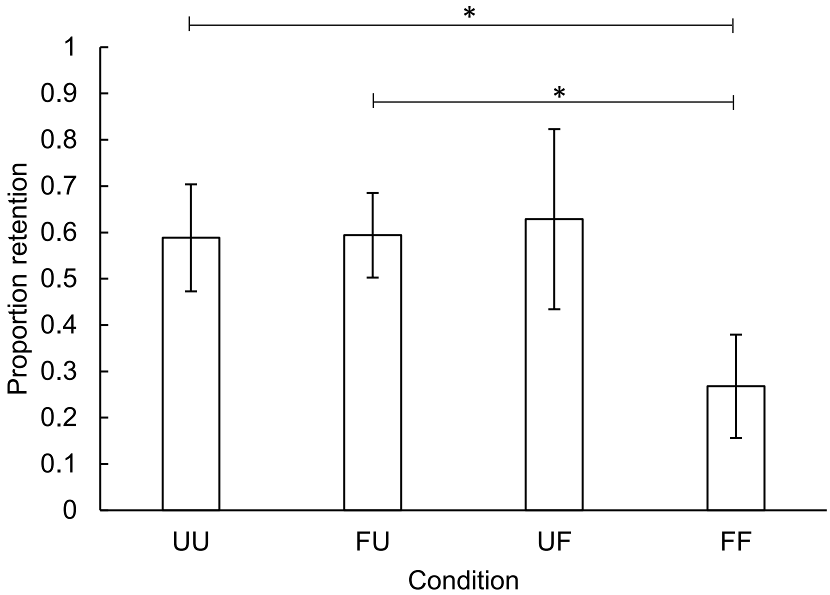


Figure 1. Experimental procedure. Distractor task consisted of a spot-the-difference task.



UU = unfilled pre-encoding delay interval – unfilled post-encoding wakeful rest

FU = filled pre-encoding delay interval – unfilled post-encoding delay interval

UF = unfilled pre-encoding delay interval – filled post-encoding delay interval

FF = filled pre-encoding delay interval – filled post-encoding delay interval

Figure 2. Mean proportion retention of amnesic patients across all experimental conditions. Proportion Retention = (Delayed Recall/Immediate Recall). Error bars represent standard error of the mean. * = $BF_{10} > 3.00$.

Supplementary material

Findings from a Sample of Healthy Controls (n =12)

Twelve healthy adults were recruited as a means of assessing performances across the current paradigm among participants that presented with no memory disorders or deficits. All participants were healthy, with normal motor skills and normal or corrected eyesight and hearing. In addition, no participants reported pre-existing cognitive impairments or any history of brain damage. Alike the amnesic patient sample, all participants from the healthy control group were native-Italian speakers. Controls were matched for age, sex, and years of education on a one-to-one basis with each patient (see Table S1). The condition order in which patients and controls were tested was also matched. There were no significant differences in age (mean age: amnesics = 53.75 years, age range = 22 – 82 years; controls = 53.75 years, age range = 22 – 82 years) or years of education (mean education: amnesics = 11.58 years, education range = 5 – 17 years; controls = 11.83 years, education range = 5 – 16 years) between the two groups ($p > .05$).

Immediate Free-Recall

Table S2 highlights the mean immediate free-recall performances of both the healthy control and amnesic patient groups across all conditions. Independent samples t-tests showed that the healthy control sample performed significantly better on each test of immediate free-recall when compared to the amnesic patient group across all conditions; UU: $t(22) = 3.645$, $p = .001$, $d = 1.488$; FU: $t(22) = 3.341$, $p = .003$, $d = 1.364$; UF: $t(22) = 4.972$, $p < .001$, $d = 2.030$; FF: $t(22) = 4.187$, $p < .001$, $d = 1.710$. Among the healthy control group specifically, immediate free-recall performance was significantly better during the UU condition in comparison to the FU condition, $t(11) = 2.923$, $p = .014$, $d = .844$. This result is more reflective of outlying performances from select participants skewing the mean within a small sample. The calculation of proportion retention mitigates differences in immediate free-recall. There were no other significant differences in immediate free-recall performance across the other conditions.

Proportion Retention

Table S3 shows the mean proportion retention of both the healthy control and amnesic patient groups across all conditions. When compared to the amnesic patient sample, there was evidence ranging from substantial to decisive that proportion retention was notable higher in the healthy control group across the UU ($BF_{10} = 7.439$, substantial evidence), FU ($BF_{10} = 23.334$, strong evidence) and FF ($BF_{10} = 351.672$, decisive evidence) conditions. While there was only anecdotal evidence to suggest the healthy control group performed better across the UF condition ($BF_{10} = .529$), this was likely due to an outlying performance of a single participant within the amnesic patient group (i.e., proportion retention > 1).

Figure S1 illustrates the mean proportion retention of the healthy control group across all conditions. Bayesian paired samples t-tests showed that there was only anecdotal evidence to suggest notable differences in proportion retention across conditions within the healthy control group ($BF_{10} < 3$).

Possible Effects of Order and Active Rehearsal

Similar to the amnesic patient group, independent-samples t-tests found no significant differences in proportion retention across the FU and UF condition based on condition order ($p > .05$). Again, these findings were further supported by independent samples t-tests which showed that uncapped proportion retention did not vary significantly across the UU and FU conditions depending on whether participants expected delayed free recall during the first testing session ($p > .05$).

Additionally, an independent samples t-test showed that proportion retention across both the UU condition and the FU condition was not significantly better for those who reported to have attempted intentional rehearsal (n = 7 for UU, n = 4 for FU) vs those who did not (n = 5 for UU, n = 8 for FU) ($p > .05$).

From these analyses, it can be reliably assumed that the distractor task suitably extinguished STM and prevented an improvement in memory retention resulting from conscious subvocal rehearsal. In turn, the assessment of uncapped proportion retention following the post-encoding delay interval was a reliable measure of retention of items from LTM.

Spot-the-Difference Task

Table S4 highlights the mean spot-the-difference task score of each group across all four trials. Bayesian independent samples t-tests showed only anecdotal evidence to suggest notable differences in mean performance across the two groups ($BF_{10} < 2$), despite conventional analyses indicating significantly better performances among the healthy control group across trials 1, 2 and 4. Given the sample size, it may be more reliable to adopt the results from the Bayesian analyses

Table S1.

Demographic information (i.e., age, sex, years of education) for all participants from each group (amnesic patients and matched controls).

Amnesic patients				Matched controls			
Participant	Age	Sex	Education	Participant	Age	Sex	Education
P1	82	m	10	C1	82	m	10
P2	54	m	13	C2	53	m	13
P3	22	f	11	C3	22	f	16
P4	52	f	8	C4	55	f	15
P5	55	m	17	C5	55	m	16
P6	57	m	13	C6	52	m	13
P7	58	f	8	C7	58	f	9
P8	32	m	13	C8	24	m	16
P9	72	m	5	C9	79	m	5
P10	42	m	13	C10	42	m	8
P11	52	f	13	C11	53	f	13
P12	67	f	15	C12	70	f	8

Note. Age and Education in years. m = male, f = female.

Table S2.

Mean immediate free-recall among each group (amnesic patients and matched controls) across all experimental conditions.

	Amnesic patients			Matched controls		
Condition	Mean	SD	SEM	Mean	SD	SEM
UU	.264	.095	.028	.448	.147	.042
FU	.194	.094	.027	.375	.162	.047
UF	.200	.096	.028	.442	.139	.040
FF	.230	.089	.026	.411	.120	.035

Note. UU = unfilled pre-encoding delay interval – unfilled post-encoding delay interval; FU = filled pre-encoding delay interval – unfilled post-encoding delay interval; UF = unfilled pre-encoding delay interval – filled post-encoding delay interval; FF = filled pre-encoding delay interval – filled post-encoding delay interval, SD = Standard deviation, SEM = Standard error of the mean.

Table S3.

Mean proportion retention (delayed free-recall/immediate free-recall) among each group (amnesic patients and matched controls) across all experimental conditions.

	Amnesic patients			Matched controls		
Condition	Mean	SD	SEM	Mean	SD	SEM
UU	.588	.400	.116	.971	.177	.051
FU	.594	.317	.091	1.051	.296	.085
UF	.629	.674	.194	.827	.191	.055
FF	.268	.387	.112	.866	.150	.043

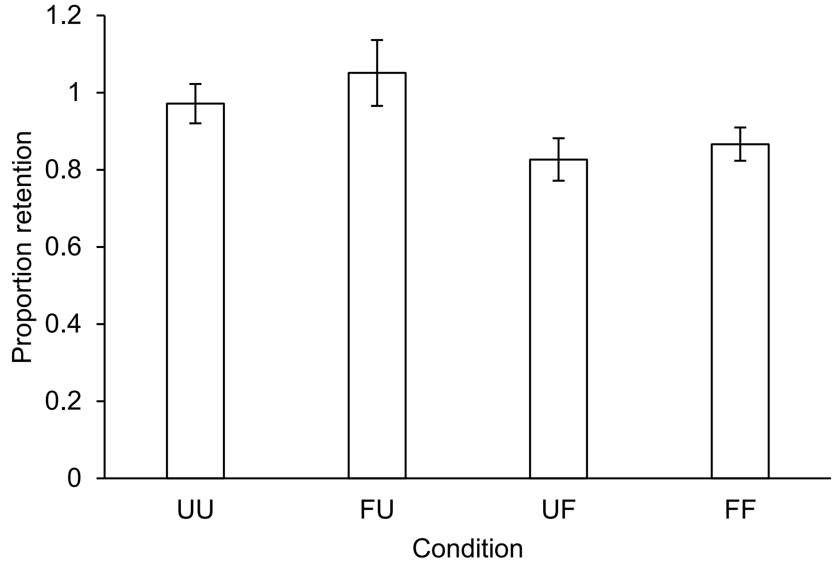
Note. UU = unfilled pre-encoding delay interval – unfilled post-encoding delay interval; FU = filled pre-encoding delay interval – unfilled post-encoding delay interval; UF = unfilled pre-encoding delay interval – filled post-encoding delay interval; FF = filled pre-encoding delay interval – filled post-encoding delay interval, SD = Standard deviation, SEM = Standard error of the mean.

Table S4.

Mean spot-the-difference task score (/36) among each group (amnesic patients and matched controls) across all trials.

	Amnesic patients			Matched controls		
Trial	Mean	SD	SEM	Mean	SD	SEM
1	.368	.175	.050	.505	.143	.041
2	.417	.165	.048	.560	.158	.046
3	.465	.162	.047	.539	.146	.042
4	.475	.166	.048	.583	.115	.033

Note. Trials 1 and 2 were undertaken during the UF and FU conditions (subject to condition order group), whereas Trials 3 and 4 were always completed during the pre- and post-encoding delay interval within the FF condition respectively. SD = Standard deviation, SEM = Standard error of the mean.



UU = unfilled pre-encoding delay interval – unfilled post-encoding wakeful rest

FU = filled pre-encoding delay interval – unfilled post-encoding delay interval

UF = unfilled pre-encoding delay interval – filled post-encoding delay interval

FF = filled pre-encoding delay interval – filled post-encoding delay interval

Figure S1. Mean proportion retention of healthy controls (n = 12) across all experimental conditions. Proportion Retention = (Delayed Recall/Immediate Recall). Error bars represent standard error of the mean.