Reminder-dependent alterations in long-term declarative memory expression

Tay, Kai Rong; Bolt, Francesca; Wong, Hei Ting; Vasileva, Svetlina; Lee, Jonathan

DOI:
10.1016/j.nlm.2023.107858

Neurobiology of Learning and Memory 206 (2023) 107858

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Reminder-dependent alterations in long-term declarative memory expression

Kai Rong Tay [a], Francesca Bolt [a], Hei Ting Wong [a,1], Svetlina Vasileva [a,2], Jonathan Lee [a,*]

[a] University of Birmingham, School of Psychology, Edgbaston, Birmingham B15 2TT, UK

ARTICLE INFO

Keywords:
Memory reconsolidation
declarative memory
reminder
interference
Working memory

ABSTRACT

The reminder of a previously-learned memory can render that memory vulnerable to disruption or change in expression. Such memory alterations have been viewed as supportive of the framework of memory reconsolidation. However, alternative interpretations and inconsistencies in the replication of fundamental findings have raised questions particularly in the domain of human declarative memory. Here we present a series of related experiments, all of which involve the learning of a declarative memory, followed 1–2 days later by memory reminder. Post-reminder learning of interfering material did result in modulation of subsequent recall at test, but the precise manifestation of that interference effect differed across experiments. With post-reminder performance of a visuospatial task, a quantitative impairment in test recall performance was observed within a visual list-learning paradigm, but not in a foreign vocabulary learning paradigm. These results support the existence of reminder-induced memory processes that can lead to the alteration of subsequent memory performance by interfering tasks. However, it remains unclear whether these effects are reflective of modulation or impairment of the putative memory reconsolidation process.

1. Introduction

Within the framework of memory reconsolidation, the reminder of a previously-learned memory can result not only in its behavioural expression (i.e. retrieval), but also in its destabilisation (Haubrich and Nader, 2018). Reminder-induced memory destabilisation leads to the necessity for memory reconsolidation in order to restabilise the memory and render it retrievable once again in the future (Sinclair and Barense, 2019; Wideman, Jardine, and Winters, 2018). Interference with memory reconsolidation can therefore cause amnesia or other forms of memory failure (Barak and Goltseker, 2021; Forcato, Argibay, Pedreira, and Maldonado, 2009; Hupbach, Gomez, Hardt, and Nadel, 2007; James, Bonsall, Hoppitt, Tunbridge, Geddes, Milton, and Holmes, 2015; Jardine, Huff, Wideman, McGraw, and Winters, 2022).

In human declarative memory settings, interference by new learning is frequently employed to disrupt memory reconsolidation (Forcato et al., 2009; Hupbach et al., 2007). However, unlike the commonly-observed decrement in memory expression observed with pharmacological reconsolidation impairment in both humans and experimental animals, the evidence using behavioural interference is more mixed. Initial studies of human declarative memory reconsolidation observed reminder-dependent alterations in memory in the form of inappropriate attribution of a second interfering learned list of items into the recall of a previously-learned list of items (Hupbach et al., 2007; Hupbach, Hardt, Gomez, and Nadel, 2008). Such “intrusions” have been argued to represent an updated memory, although there was no quantitative impairment in the number of items recalled from the first list. This pattern contrasts somewhat with studies employing paired-associate learning (Forcato et al., 2009; Forcato, Burgos, Argibay, Molina, Pedreira, and Maldonado, 2007), in which the memory effect was a true impairment in retrieval/expression, with no evidence for any intrusions. Memory impairments were also observed in neutral autobiographical memories, when interfered with by the learning of a novel story immediately after retrieval (Schwabe and Wolf, 2009; Wichert, Wolf, and Schwabe, 2013). Importantly, these patterns of results are largely replicated, at least at a conceptual level, within these research groups.

While a recent *meta*-analysis provides overall support for the existence of human declarative memory reconsolidation (Scully, Napper,

* Corresponding author.
E-mail address: j.l.c.lee@bham.ac.uk (J. Lee).

[1] Current address: Department of Social and Behavioural Sciences, City University of Hong Kong, Tat Chee Avenue, Kowloon, Hong Kong SAR.

[2] Current address: The Queensland Brain Institute, University of Queensland, St Lucia QLD 4072, Australia.

https://doi.org/10.1016/j.nlm.2023.107858
Received 3 May 2023; Received in revised form 20 October 2023; Accepted 6 November 2023
Available online 7 November 2023
1074-7427/

and Hupbach, 2016), it was not limited to interference interventions and nor did it account for the qualitatively different nature of reconsolidation effects (intrusions vs retrieval impairment). The *meta*-analysis also preceded the publication (Klingmuller, Caplan, and Sommer, 2017) of a failure to replicate the original Hupbach et al (2007) study which, in the context of other high-profile failures to replicate reconsolidation observations in both humans (Chalkia, Schroyens, Leng, Vanhasbroeck, Zenses, Van Oudenhove, and Beckers, 2020; Hardwicke, Taqi, and Shanks, 2016; Levy, Mika, Radzyminski, Ben-Zvi, and Tibon, 2018; Stemerding, Stibbe, van Ast, and Kindt, 2022; van Schie, van Veen, van den Hout, and Engelhard, 2017) and rodents (Luyten and Beckers, 2017; Schroyens, Alfei, Schnell, Luyten, and Beckers, 2019), demands further exploration.

Given the uncertainty around the reliability of post-reminder interference effects in human declarative memory, and ultimately the existence of human declarative memory reconsolidation at all, we have conducted a series of experiments. These began initially with further attempts to replicate Hupbach et al (2007), and then broadened to encompass different natures of learning and impairment. Specifically, we extended to the use of foreign vocabulary word learning (Potts and Shanks, 2012), using memory reminder followed by interference with new learning. We then proceeded to use a visuospatial intervention that has consistently resulted in reconsolidation impairments characterised as a quantitative decrease in memory expression (James et al., 2015; Kessler et al., 2020), and may be more likely to result in disruptions to the biological mechanisms of memory reconsolidation in a manner similar to cellular or pharmacological interventions. Of note, the hypothesised competition for visual working memory resources engendered by the visuospatial working memory task (James et al., 2015) parallels the suggested mechanism by which a distractor displaces the representation of a reminded fear memory in rats from working memory to impair its reconsolidation (Crestani, Zacouteguy Boos, Haubrich, Ordoñez Sierra, Santana, Molina, Cassini, Alvares, and Quillfeldt, 2015). We observe discrepant results, but overall provide support for the existence of a reminder-dependent memory process in human declarative memories.

2. Methods

2.1. Experimental design

Research participants and experimental design are described below. Participants were randomly allocated to experimental group, using an independent random sequence generator or block randomisation within Qualtrics. Experimenters were not strictly blinded to allocation during the conduct of the experiments, but all data processing and analysis was conducted blind to the intervention.

2.2. Participants

399 undergraduate students from the University of Birmingham completed participation across all experiments. All participants were recruited through the Psychology Research Participation Scheme and received course credit for their participation; the only criterion for inclusion was an absence of visual impairment. Participants gave their informed consent prior to each session of participation, and all procedures were approved by the University of Birmingham Science, Technology, Engineering and Mathematics (STEM) Ethics Review Committee.

2.3. Behavioral procedures

2.3.1. Experiment 1.1

30 participants were tested individually in person across 3 days. On day 1 all participants were greeted by an experimenter and were seated at a desktop computer. A powerpoint presentation of 20 everyday objects (list 1) was presented. The images advanced automatically every 15 s. Participants were instructed to look closely at each presented object and named them aloud. At the end of the object presentation phase, participants verbally recalled as many objects as possible. This procedure was repeated until the participants either successfully remembered 17 images out of 20 images (85 % correct) or underwent a maximum of four learning trials. Throughout the whole free recall session, the experimenter manually recorded all the participants' responses.

On day 2 (48 h after day 1) participants in the reminder group were shown to the same room as day 1 by the same experimenter. They were asked if they remembered the procedure of day 1 but did not explicitly recall any of the objects. Participants in the no reminder group were shown to a different room in a different building, with a different computer, by a different experimenter to day 1. The reminder and no reminder participants were then presented with a second list of objects. Similarly to previous studies (Hupbach et al., 2007; Hupbach et al., 2008; Klingmuller et al., 2017), the procedure differed from day 1 so that it would not act as a reminder. The objects in list 2 were presented all at once on a single powerpoint slide. Participants named each of the objects and studied them for a total of 5 min, after which they verbally recalled as many objects as possible. A similar learning procedure and criterion was implemented as for day 1 learning, but with the re-learning time limited to 30 s. Participants in the no interference control group did not participate in day 2.

On day 3 (48 h after day 2) all participants were greeted by the same experimenter and shown to the same room as day 1. Participants recalled as many objects from day 1 as possible. When no more objects could be recalled, participants read aloud a paragraph of prose and then recalled as many objects as possible again.

Following a delay of 8 weeks, all participants were re-invited for further testing, and 18 took part. Participants were unaware that they would be re-invited for further testing. This was to reduce the likelihood of any rehearsal or other techniques being adopted to aid future performance. Participants were greeted by the same experimenter as in the initial part of the study and shown to the same room in which they initially recalled the test objects (day 3). Participants verbally recalled as many objects from list 1 as possible. When no more objects could be recalled, participants read aloud the same paragraph of prose from the first part of the study and attempted to recall as many objects as possible once again.

2.3.2. Experiment 1.2

108 participants were tested individually in person across 3 days. The estimated effect size for the correlation between list 1 recall and list 2 intrusions in Experiment 1.1 was 0.22. In order to achieve power of 0.9, group sizes of 33 were required. The procedure was similar to that employed in Experiment 1.1, with the following alterations. The object images were taken randomly from the exemplar pairs paradigm of Brady et al (2008). Learning time on day 1 was reduced to 4 s per image, and a post-learning mathematical distraction task was implemented for 3 min prior to recall, which maintained a similar interval between the first image presentation and recall as in Experiment 1.1. The reminder group on day 2 returned to the same context and were met by the same experimenter as on day 1, but were not asked the reminder question. Learning on day 2 involved presentation of a single A4 sheet of paper showing all 20 images for 30 s. Testing on day 3 involved 4 repeated tests. There was no additional remote memory test.

2.3.3. Experiment 1.3

12 participants were tested individually in person across 2–3 days, using the same learning and final test procedures as in Experiment 1.2. The reminder group received the reminder procedure on day 2, but did not learn any interfering material. The no-reminder group did not participate in day 2.

2.3.4. Experiment 2

109 participants were tested in groups of up to 10 across 3 days. The participants remained within their group setting consistently across days. On day 1 all participants were greeted by an experimenter in a group study room and given a list of 40 English-Swahili word pairs (adapted from Karpicke and Roediger, 2008) to learn for 40 min. They were then given a 15-min paper test, in which they had to write the Swahili translation for each of the 40 English words.

On day 2 (48 h after day 1) participants returned to a similar group study room in the same building as on day 1, with the same experimenter. Participants in the reminder conditions completed another 15-min paper test of translation of the 40 English words into Swahili (the order of word presentation was different to the day 1 test). Participants in the interference conditions were given the Maori translations of the same 40 English words to learn for 40 min. A mathematical distractor task was performed for 10 min after reminder and/or before interference. The 2 × 2 factorial design involved the presence or omission of the reminder and interference phases.

On day 3 (48 h after day 2) participants again returned to a similar group study room with the same experimenter. All participants completed a final 15-min paper English-Swahili translation test (with a new order of word presentation).

Answers in the tests were marked as correct only if the spelling of the Swahili word was exactly as presented in the original learning list.

2.3.5. Experiment 3.1

54 participants completed the 3 days of testing online via Qualtrics. On day 1, participants were presented with the same images as in Experiment 1.2, sequentially each for 4 s, and were instructed to memorise the images for a later test. Following successful completion of an attention check question, the participants performed a free recall test. In contrast to the in-person experiments (1.1 & 1.2), there was no criterion of test performance or opportunity for repeated learning.

On day 2 (24–48 hr after day 1), participants in the reminder condition were asked to write a brief account of what they did on day 1 without giving precise detail. Participants in the test condition completed a free recall test of the images learned on day 1. Participants in the no-reminder condition proceeded directly to the next phase of the day 2 procedure. In this next phase, participants were either directed to play an online Tetris game for up to 15 min or to watch an online ink drop video that lasted for 12 min.

On day 3 (24–48 hr after day 2), all participants performed a free recall test and then were asked if there were any reason that their data should be excluded (e.g. due to cheating or not following instructions). Participants were informed that they would receive the advertised study credit regardless of the response to these final questions.

One participant reported cheating and 2 participants in the reminder condition listed the images in their account of day 1. Finally, 2 participants performed < 25 % accuracy on the day 1. These 5 participants were removed from the data analysis.

2.3.6. Experiment 3.2

86 participants completed the 3 days of testing online via Qualtrics. On day 1, participants were presented with the same Swahili-English word pairs as in Experiment 2, all on a single screen presentation for 20 min, and were instructed to memorise the translations for a later test. Following successful completion of an attention check question, the participants performed a test, in which each of the 40 Swahili words was presented and the English translation had to be typed into the response field.

On day 2 (24–48 hr after day 1), participants in the reminder condition were asked to write a brief account of what they did on day 1 without giving precise detail. Participants in the test condition completed a further Swahili-to-English test of all 40 words. Participants in the no-reminder condition proceeded directly to the next phase of the day 2 procedure. In this next phase, participants were either directed to play an online Tetris game for up to 15 min or to watch an online ink drop video that lasted for 12 min.

On day 3 (24–48 hr after day 2), all participants performed a final Swahili-to-English test of all 40 words and then were asked if there were any reason that their data should be excluded (e.g. due to cheating or not following instructions). Participants were informed that they would receive the advertised study credit regardless of the response to these final questions.

No participants were excluded from the statistical analyses.

2.4. Statistical analysis

No outliers were excluded from the analyses (all data fell within 2 sd of the mean). Reported endpoints and statistical analytical approach were determined prospectively. Statistical analyses were conducted and Boxplots generated in JASP (JASP Team, 2016). η_p^2 was used as an estimate of effect size.

Final retrieval test performance was analysed using one-way or factorial ANOVA. Where there were test repeats (Experiments 1.1, 1.2 & 1.3), mean performance across the repeats was used as a single primary outcome. In these same experiments, accurate retrieval of list 1 items were analysed independently of erroneous intrusions of list 2 items into list 1 recall. In experiment 2, between groups factors of test (vs no test) and interference (vs no interference) were used in full factorial analyses of test performance on days 1 & 3 independently. This approach was used because of the conceptual similarity to experiments 1.2, in which day 1 retrieval was confounded by the opportunity for repeated learning and so could not be analysed meaningfully. In Experiments 3.1 & 3.2, a full factorial analysis across days 1 & 3 was conducted with factors reminder (vs no reminder & test), tetris (vs video) and session. Significant main effects were explored with Tukey-corrected post-hoc pairwise comparisons; significant interactions were explored with analyses of simple main effects.

3. Results

3.1. Experiment 1.1

Our initial experiments consisted of a conceptual replication of Hupbach et al (2007), using visual image list learning instead of physical object presentation. We observed that there were no differences between the experimental groups in their correct recall of list 1 items across both recall trials (Fig. 1A; Group: $F(2,27) = 1.06$, $p = 0.36$, $\eta_p^2 = 0.073$; Group × Trial: $F(2,27) = 0.87$, $p = 0.43$, $\eta_p^2 = 0.061$). All groups performed better on the 2nd recall trial than on the 1st (Trial: $F(1,27) = 19.8$, $p < 0.001$, $\eta_p^2 = 0.42$). In contrast, there was a difference between the groups in the number of intrusions of list 2 items into list 1 recall (Fig. 1B; Group: $F(2,27) = 36.0$, $p < 0.001$, $\eta_p^2 = 0.73$; Group × Trial: $F(2,27) = 0.40$, $p = 0.67$, $\eta_p^2 = 0.029$), with no change in intrusion rate between recall trials (Trial: $F(1,27) = 0.40$, $p = 0.53$, $\eta_p^2 = 0.015$). Post-hoc comparisons confirmed that the reminder group had greater numbers of intrusions than both of the other groups. An additional analysis of the total number of items reported showed no differences between the groups (Group: $F(2,27) = 0.82$, $p = 0.45$, $\eta_p^2 = 0.057$; Group × Trial: $F(2,27) = 0.80$, $p = 0.46$, $\eta_p^2 = 0.056$). However, there was no indication that the number of correctly-recalled items was negatively correlated with the number of intrusions, either across the whole sample ($r = -0.11$, $p = 0.29$) or just within the reminder group ($r = 0.34$, $p = 0.83$).

In an exploratory follow-up, we re-tested a subset of the same participants (n = 6 per group) 8 weeks after the first test. There were again no differences between the groups in correct list 1 recall (Fig. 1C; Group: $F(2,15) = 0.52$, $p = 0.61$, $\eta_p^2 = 0.065$; Group × Trial: $F(2,15) = 6.24e-31$, $p = 1.0$, $\eta_p^2 = 0.000$). All groups performed slightly worse on the 2nd recall trial than on the 1st (Trial: $F(1,15) = 7.50$, $p = 0.015$, $\eta_p^2 = 0.33$). Again, there was a difference between the groups in the number of intrusions of list 2 items into list 1 recall (Fig. 1D; Group: $F(2,157) = 28.8$,

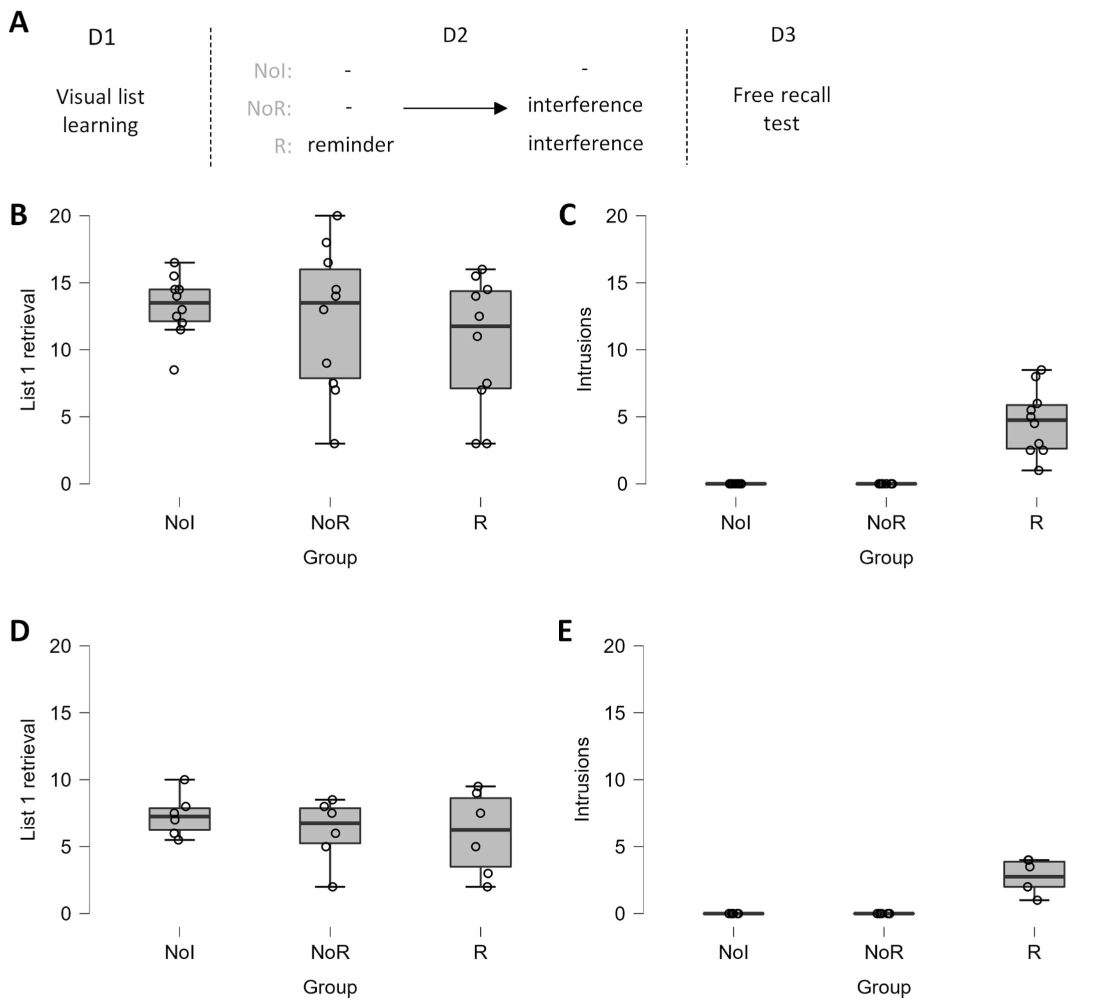

Fig. 1. Memory reminder in combination with interference learning results in greater intrusions at test. **A,** Experimental schematic: participants learned an initial visual List 1 and then were split into groups that received no interference (NoI; n = 10), No reminder + interference (NoR, n = 10) or reminder + interference (R, n = 10). **B,** Retrieval of List 1 items at the test 2 days after reminder/interference. No obvious differences were observed between the groups. **C,** Intrusions of List 2 items into List 1 retrieval 2 days after reminder/interference. Intrusions were only observed in the reminder group. **D,** Retrieval of List 1 items at the test 8 weeks after the first test (n = 6 per group). No obvious differences were observed between the groups. **E,** Intrusions of List 2 items into List 1 retrieval 8 weeks after the first test. Intrusions were only observed in the reminder group.

$p < 0.001$, $\eta_p^2 = 0.79$; Group × Trial: $F(2,15) = 1.00$, $p = 0.39$, $\eta_p^2 = 0.12$), with no change in intrusion rate between recall trials (Trial: $F(1,15) = 1.00$, $p = 0.33$, $\eta_p^2 = 0.062$). Post-hoc comparisons confirmed that the reminder group had greater numbers of intrusions than both of the other groups.

We further analysed mean performance at re-test compared to that at initial test. Recall performance declined from initial test to re-test ($F(1,15) = 46.4$, $p < 0.001$, $\eta_p^2 = 0.76$), as did the number of intrusions (Test: $F(1,15) = 11.1$, $p = 0.005$, $\eta_p^2 = 0.43$; Test × Group: $F(2,15) = 11.1$, $p = 0.001$, $\eta_p^2 = 0.60$).

These results replicate statistically the previous observations by Hupbach et al (2007), extending them to show long-term retention of the aberrant intrusions in the face of time-dependent memory decline. However, we note that the quantitative level of recall performance was greater in the present study compared to Hupbach et al (2007), and the number of intrusions was substantially lower. Moreover, we observed no intrusions in any participant within the no-interference and no-reminder groups, which differs from both Hupbach et al (2007) and the failed replication by Klingmuller et al (2017). Given that a single positive replication, especially with unexpectedly-high levels of performance, would not be sufficient evidence alone to renew confidence in replicability of the Hupbach et al (2017) intrusion effect, we sought to conduct a further replication, capitalising on observations that alterations to the learning procedure had reduced memory performance in parallel experiments.

3.2. Experiment 1.2

Using a different set of visual images, taken from a set of standardised images (Brady et al., 2008), and a larger sample size that would be sufficiently powered to detect a correlation between numbers of recalled items and intrusions, we observed a difference between the groups in average list 1 recall at test (Fig. 2A; $F(2,105) = 6.89$, $p = 0.002$, $\eta_p^2 = 0.12$). Post-hoc comparisons revealed that the no-reminder group recalled fewer list 1 items than the no-interference and reminder groups, which did not differ from each other. In contrast, while there was also an effect of group on the number of intrusions (Fig. 2B; $F(2,105) = 33.61$, $p < 0.001$, $\eta_p^2 = 0.39$), this was driven by there being no intrusions in the no interference groups, but similar numbers of intrusions in the no-reminder and reminder groups. Therefore, the reminder resulted in higher recall, but no difference in intrusions, as compared to the no-reminder group.

A correlation analysis of recall against intrusions revealed a significant negative correlation when the whole sample (i.e. all groups) was analysed together ($r = -0.30$, $p < 0.001$). Analyses by experimental group showed that while there was a negative correlation in the no-

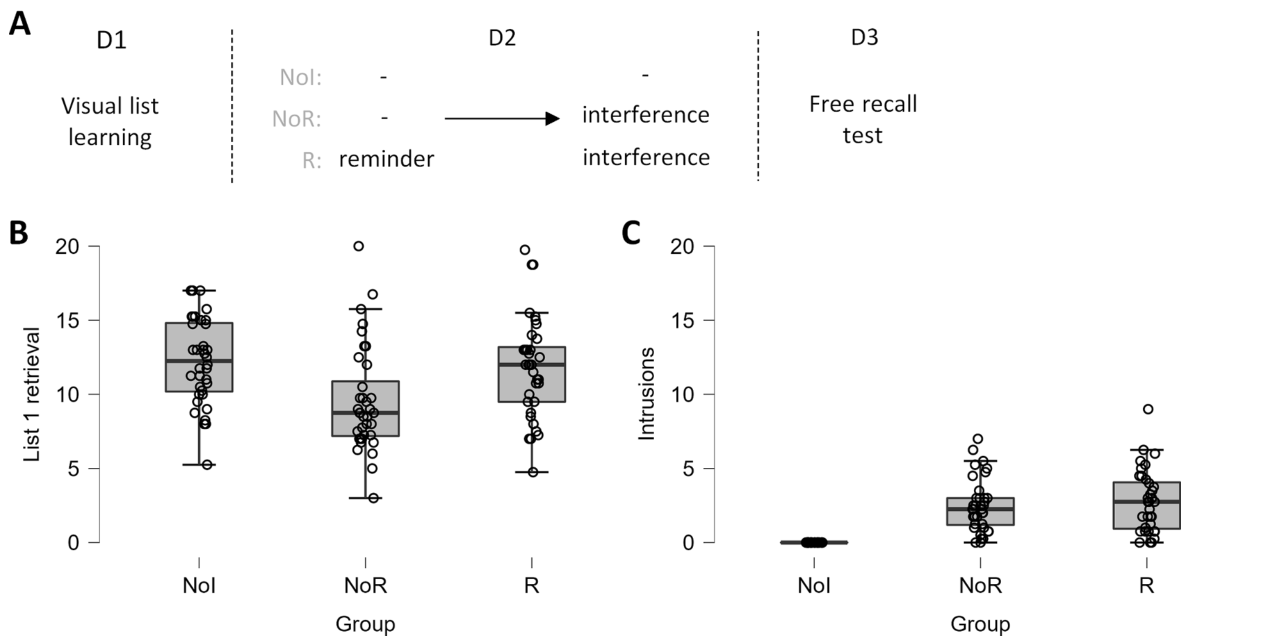

Fig. 2. Memory reminder in combination with interference learning results in protection from interference in visual list learning. **A,** Experimental schematic: participants learned an initial List 1 and then were split into groups that received no interference (NoI; n = 36), No reminder + interference (NoR, n = 36) or reminder + interference (R, n = 36). **B,** Retrieval of List 1 items at the test 2 days after reminder/interference. Performance was reduced in the no reminder group compared to the reminder and no interference groups. **C,** Intrusions of List 2 items into List 1 retrieval 2 days after reminder/interference. Similar numbers of intrusions were observed in the no reminder and reminder groups; no intrusions were observed in the no interference group.

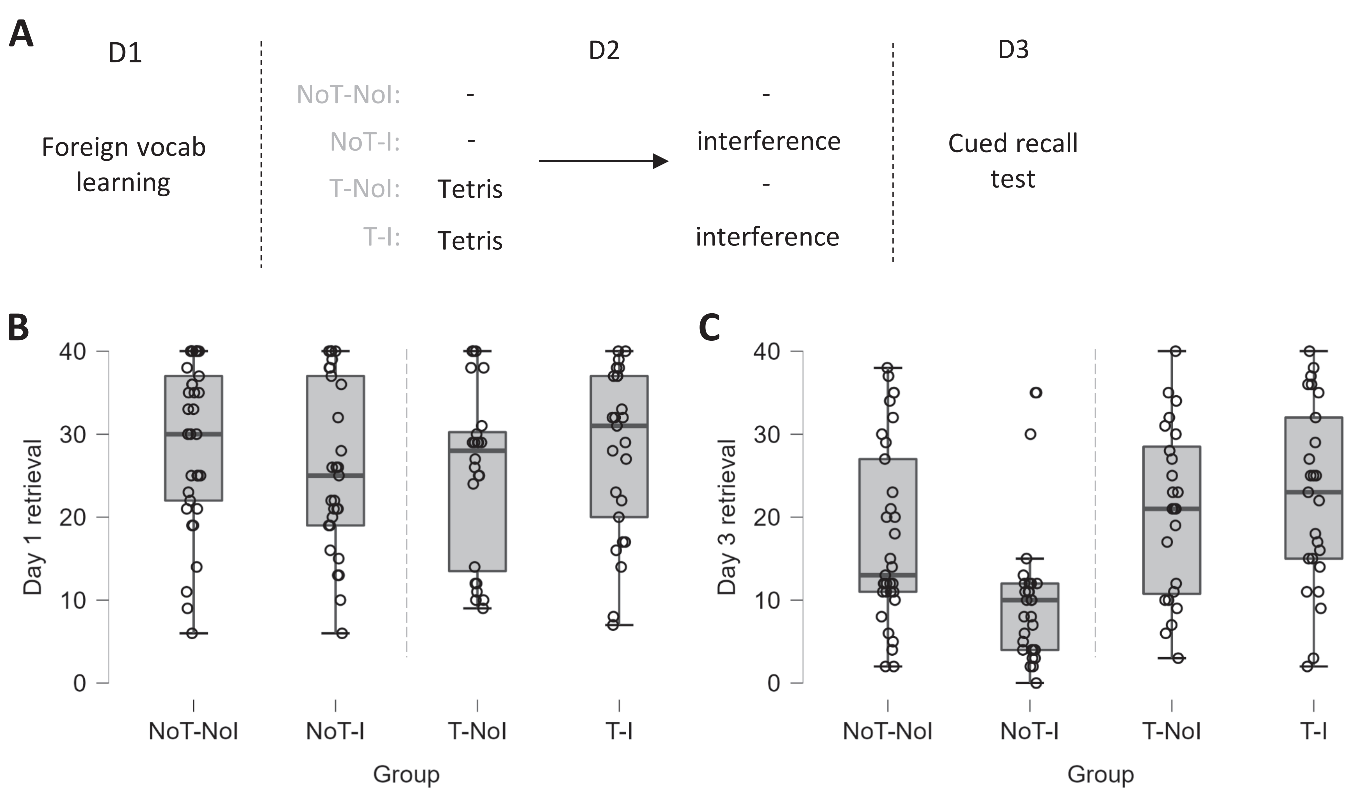

Fig. 3. Memory test in combination with interference learning results in protection from interference in foreign vocabulary learning. **A,** Experimental schematic: participants learned a list of English-Swahili translations and then were split into groups that received no test or Maori interference learning (NoT-NoI; n = 33), No test + interference (NoT-I, n = 29), Test and no interference (T-NoI, n = 24) or Test + interference (T-I, n = 25). **B,** Similar test performance was observed immediately after initial learning on day 1. **C,** At the retrieval test after reminder/interference, performance in the no test + interference group was lower than both the no test + no interference and test + interference groups.

reminder group ($r = -0.38$, $p = 0.012$), the correlation was absent in the reminder group ($r = -0.21$, $p = 0.11$). There were no intrusions in the no-interference group.

3.3. Experiment 1.3

The effect of the reminder to increase list 1 recall compared to the no-reminder group is reminiscent of a retrieval practice effect, albeit in the presence of interfering learning. This contrasts with the failure to observe a retrieval practice effect with a reminder alone in the absence of any interference (Klingmuller et al.,2017). Therefore, we employed our experimental materials to determine whether our reminder alone was able to increase later recall. A reminder group was compared to a group that had no experimental session between initial learning and final test. There was no difference in recall at test between the groups (mean ± SEM; no reminder = 9.68 ± 0.56; reminder = 9.20 ± 1.16; $t(10) = 0.45$, $p = 0.66$, $d = 0.26$).

3.4. Experiment 2

The results of experiment 1.2 are an effective conceptual replication of Potts & Shanks' (2012) immunisation against interference by reminder, whereby a reminder test protected against the disruptive effect of interference. Therefore, we sought to provide a close conceptual replication of Potts & Shanks (2012), in order confirm the similarity of observations across experimental paradigms.

There was no difference between the groups in initial learning of the English-Swahili vocabulary pairs, as evidenced by post-learning recall performance (data not shown; test × interference: $F(1,107) = 2.00$, $p = 0.16$, $\eta_p^2 = 0.018$; test: $F(1,107) = 0.18$, $p = 0.67$, $\eta_p^2 = 0.002$; interference: $F(1,107) = 0.022$, $p = 0.88$, $\eta_p^2 = 0.00$).

At the final test on day 3, there was evidence for a differential impact of interference depending on whether participants had previously been tested (Fig. 3; test × interference: $F(1,107) = 5.33$, $p = 0.023$, $\eta_p^2 = 0.047$; interference: $F(1,107) = 1.94$, $p = 0.17$, $\eta_p^2 = 0.018$), with an overall effect of prior testing to elevate final performance ($F(1,107) = 14.6$, $p < 0.001$, $\eta_p^2 = 0.12$). Analyses of simple main effects revealed that interference impaired performance in the absence of prior testing ($F = 7.74$, $p = 0.006$), but not when participants were tested prior to interfering learning ($F = 0.38$, $p = 0.54$). Analysis of the orthogonal simple main effect of prior testing revealed no effect in the absence of interference ($F = 1.16$, $p = 0.28$), but a significant protection against interference ($F = 18.5$, $p < 0.001$).

We conducted an exploratory analysis of these data to analyse them in the same way as Experiment 1.2 (omitting the test-no interference group). There was a significant difference between the groups in test recall ($F(2,84) = 9.51$, $p < 0.001$, $\eta_p^2 = 0.19$). Post-hoc comparisons ($p < 0.05$) revealed the same pattern of group differences, with the no-reminder (no test + interference) group performing at a lower level than the no interference (no test + no interference) and reminder (test + interference) equivalent groups. The latter 2 groups did not differ from each other. Therefore, the effect of reminder/test to perform better than no reminder/no test, in the presence of interfering learning, is similar across visual list learning and foreign vocabulary learning paradigms.

3.5. Experiment 3.1

While the reminder-induced immunisation of memory against interference might be underpinned by reconsolidation processes, it is clear from the previous experiments that post-reminder interference does not typically result in impairment of recall of the originally-learned declarative memory, at least not in visual list learning or foreign vocabulary learning settings. Therefore, we sought to translate the application of visuospatial working memory taxation (James et al., 2015) to the disruption of emotionally-neutral declarative memory reconsolidation.

Using an online implementation of our visual list-learning procedure from Experiment 1.2, groups of participants were briefly reminded, fully tested or received no reminder prior to playing tetris or watching a colourful video. There was evidence for an effect of playing tetris depending on the reminder condition (Fig. 4; reminder × tetris × session: $F(2,68) = 7.36$, $p = 0.001$, $\eta_p^2 = 0.18$; reminder × tetris: $F(2,68) = 1.32$, $p = 0.27$, $\eta_p^2 = 0.037$). Analyses of simple main effects of tetris at different sessions under the different reminder conditions revealed an effect at the day 3 final test in the reminder condition ($F = 7.42$, $p = 0.012$), and not at any of the other tests ($F < 2.16$, $p > 0.15$).

3.6. Experiment 3.2

In order to test whether the amnestic impact of post-reminder playing of tetris generalised across declarative memory paradigms, we studied its impact in an online implementation of our foreign vocabulary learning procedure from Experiment 2, using the same 3 reminder conditions as in Experiment 3.1. There was no strong evidence for an effect of playing tetris depending on the reminder condition (Fig. 5; reminder × tetris × session: $F(2,80) = 0.13$, $p = 0.88$, $\eta_p^2 = 0.003$; reminder × tetris: $F(2,80) = 1.49$, $p = 0.23$, $\eta_p^2 = 0.036$; tetris × session: $F(1,80) = 1.95$, $p = 0.17$, $\eta_p^2 = 0.024$; tetris: $F(1,80) = 1.25$, $p = 0.27$, $\eta_p^2 = 0.015$). Analyses of simple main effects of tetris at different sessions under the different reminder conditions revealed little evidence for an effect at any of the tests ($F < 1.87$, $p > 0.18$; day 3 final test in the full test reminder condition: $F = 3.24$, $p = 0.083$).

4. Discussion

In the present study, we have observed a number of reminder-dependent effects in visual list learning and foreign vocabulary learning settings. Reminder of a visual list prior to the learning of a new interfering list of visual images resulted in one experiment in a long-lasting pattern of intrusions of list 2 items into list 1 recall, but with no quantitative impairment in list 1 recall. However, in another experiment, reminder instead protected against the effect of list 2 interfering learning to impair list 1 recall. This latter pattern was replicated in the foreign vocabulary learning setting. Finally, performance of a visuospatial task following memory reminder impaired subsequent retrieval of a visual list memory, but not foreign vocabulary memory.

Our two experiments on post-reminder interference in visual list learning both show reminder-dependent effects that may be consistent with engagement of memory reconsolidation processes. The pattern of intrusions in Experiment 1.1 replicates a number of previous studies (Capelo, Albuquerque, and Cadavid, 2019; Hupbach et al., 2007; Hupbach et al., 2008; Scully et al., 2016), while extending them to demonstrate that the altered pattern of memory expression lasts for many weeks. Typically, the final test occurs only days after reminder and interference learning (Hupbach et al., 2007; Klingmuller et al., 2017; Levy et al., 2018). However, we did not test recall of list 2 in order to evaluate the presence or absence of intrusions of list 1 items. Therefore, we cannot substantiate an asymmetric pattern of intrusions that has been argued to be supportive of a reconsolidation-based explanation (Hupbach, Gomez, and Nadel, 2009). Nevertheless, plausible alternative accounts of this asymmetry, such as the temporal context model (Gershman, Schapiro, Hupbach, and Norman, 2013; Sederberg, Gershman, Polyn, and Norman, 2011) mean that reminder-dependent effects of memory interference cannot necessarily be taken as strongly supportive of a reconsolidation process.

The uncertainty concerning the interpretation of intrusions may be less applicable to our second pattern of results, observed in both list learning (Experiment 1.2) and foreign vocabulary learning (Experiment 2). In these experiments, reminder appeared to protect or immunise against interference. This replicated a previous observation in foreign vocabulary learning (Potts and Shanks, 2012), but to our knowledge extended it for the first time into visual list learning. While the temporal

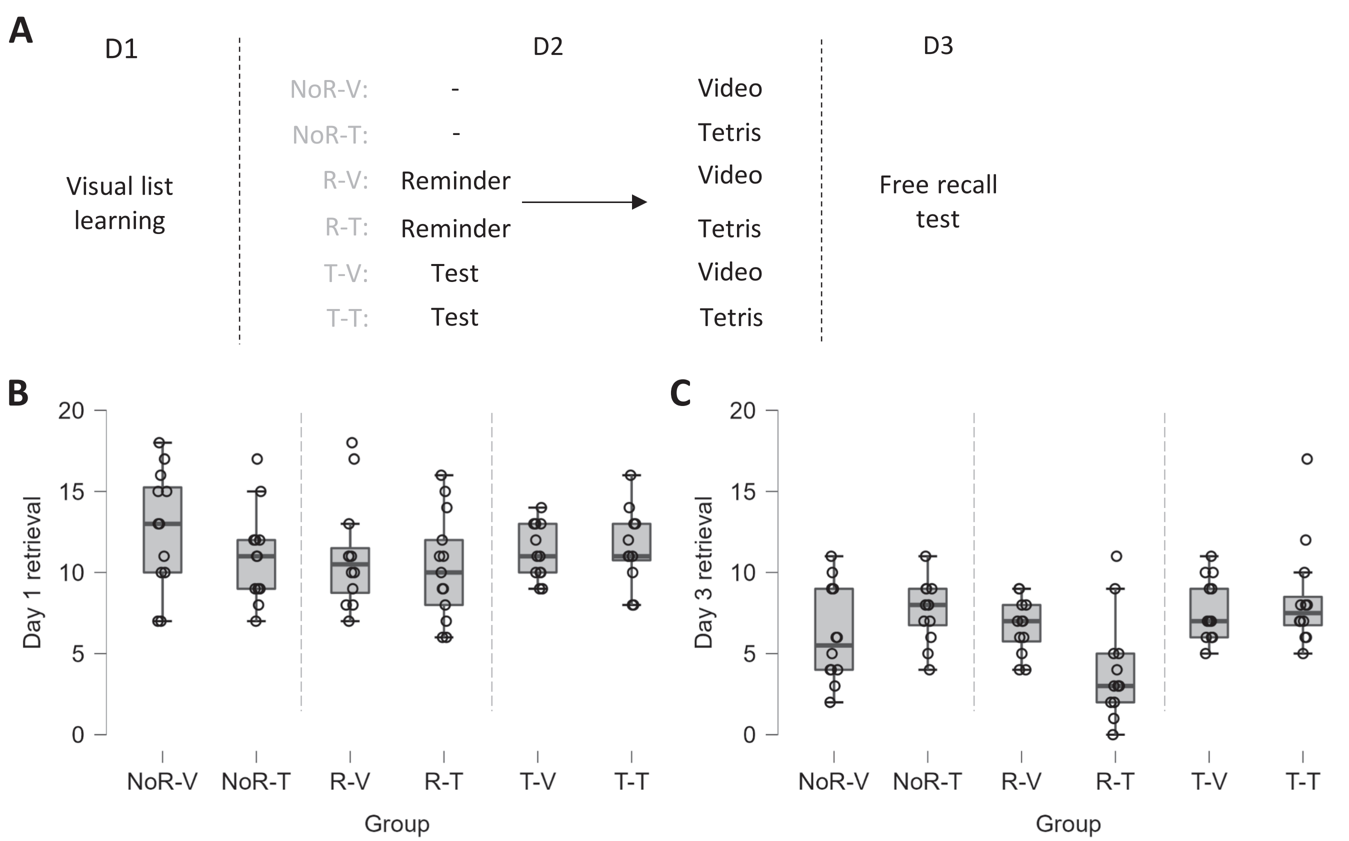

Fig. 4. Performance of a visuospatial task impaired retrieval of a visual list only when combined with memory reminder. **A,** Experimental schematic: participants learned a list of visual images and then were split into groups that received no reminder (NoR-), a brief reminder (R-) or a retrieval test (T-). They then either watched a video (-V) or played tetris (-T). **B,** Similar test performance was observed immediately after initial learning on day 1. **C,** At the retrieval test after reminder/tetris, performance in the reminder + tetris group was lower than other tetris groups and the reminder + video group (n = 12 per group; n = 13 for groups R-T & T-V).

context model might not immediately account for protection against interference, it is also not obvious that memory reconsolidation need be invoked. Reminder can not only result in memory destabilisation/reconsolidation, but also in retrieval practice effects (Karpicke and Roediger, 2008; Roediger and Karpicke, 2006), or indeed no overt alteration in the memory at all. However, our list memory reminder procedure did not result in an obvious retrieval practice effect (Experiment 1.3) and the vocabulary test that acted as a reminder in Experiment 2 also showed no evidence of producing a testing effect. While it is possible that the quantitative absence of a testing effect in the absence of interference does not exclude the presence of a testing effect that emerges under conditions of greater test difficulty (Halamish and Bjork, 2011; Potts and Shanks, 2012), the quantitative levels of performance in our experiments was not high. Therefore, it is perhaps unlikely that the equivalent list 1 retrieval performance in our reminder + interference vs no interference groups reflects a simple offsetting of retrieval-mediated memory enhancement against interference-generated memory impairment. Instead, some other retrieval-engaged process might account for the protection against interference. It is also pertinent to note that the absence of obvious retrieval-practice effect in our experiments does not conflict with previous observations; it is simply the case that under the test conditions and parameters used in our procedures, there is little evidence that the prior reminder enhances performance *per se*. Indeed, the mechanisms underpinning when a reminder enhances a memory, compared to opening it up for impairment, are not well understood; they may include differences in the timing of neural recruitment (St Jacques, Olm, and Schacter, 2013).

It is reminder-dependent quantitative memory impairments that are typically interpreted as a disruption of memory reconsolidation (Forcato et al., 2009; Forcato et al., 2007; Haubrich and Nader, 2018; Schwabe and Wolf, 2009; Wichert et al., 2013). Therefore, it is not initially obvious that reminder-induced protection against interference might be a result of memory destabilisation/reconsolidation. However, studies in rats have shown that the reminder of a hippocampal-dependent memory maintained the precision of the memory (which typically decays over time), in a manner that was dependent upon neural mechanisms of memory destabilisation (De Oliveira Alvares, Crestani, Cassini, Haubrich, Santana, and Quillfeldt, 2013; de Oliveira Alvares, Einarsson, Santana, Crestani, Haubrich, Cassini, Nader, and Quillfeldt, 2012). Moreover, the effect of repeated memory reminder to strengthen hippocampal memory generalises from rodents (De Oliveira Alvares et al., 2013) to humans (Forcato, Rodriguez, and Pedreira, 2011). As a result, it is not implausible that a reconsolidation-based process that is triggered by memory reminder might, at least under certain conditions, maintain the precision and strength of a declarative memory in the face of interference. It is important here to reiterate that while we have observed conceptually-similar patterns in experiments 1.2 & 2, the two paradigms differ in the nature of the reminder. In the list-learning experiments, the reminder involved re-exposure to the learning context, experimenter and a reminder question, whereas it was an explicit retrieval test in the foreign vocabulary experiments. First, it is established in experimental animals that the capacity of memory reminder to trigger reconsolidation is not dependent upon behavioural expression of the memory (Ben Mamou, Gamache, and Nader, 2006; Frenkel, Maldonado, and Delorenzi, 2005). Moreover, given that a “full reminder”, comprising cued retrieval and production of the answer, has been shown not to trigger declarative memory reconsolidation, at least in a paired-associate memory task (Forcato et al., 2009), we might conclude that the vocabulary test also might not successfully engage destabilisation and reconsolidation. Another potentially-important methodological

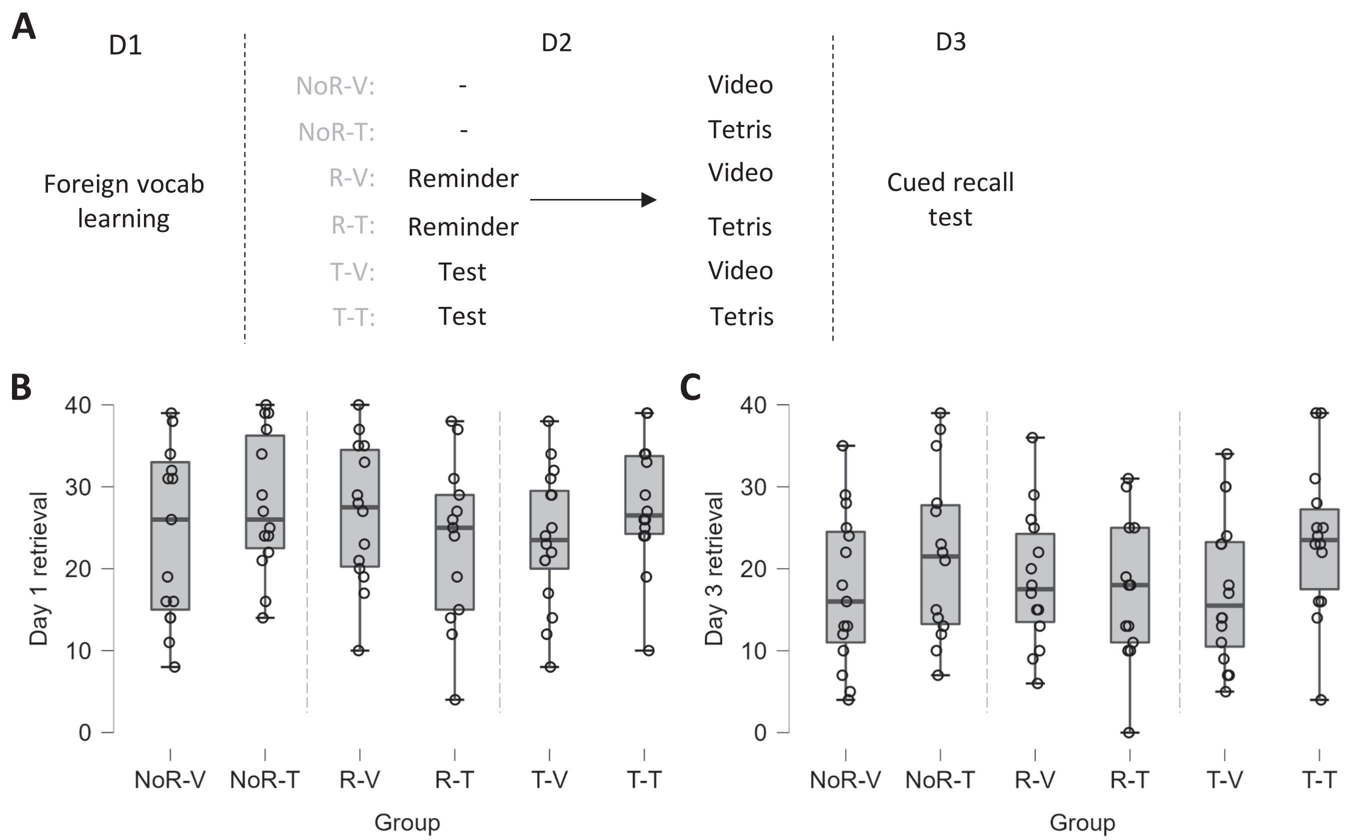

Fig. 5. Performance of a visuospatial task did not affect retrieval of English-Swahili vocabulary learning. **A,** Experimental schematic: participants learned a list of English-Swahili word pairs and then were split into groups that received no reminder (NoR-), a brief reminder (R-) or a retrieval test (T-). They then either watched a video (-V) or played tetris (-T). **B,** Similar test performance was observed immediately after initial learning on day 1. **C,** Similar test performance was also observed after reminder/tetris (n = 14 per group; n = 13 for group R-T; n = 15 for group NoR-V; n = 16 for group T-V).

difference is that there was a criterion of learning implemented in experiment 1.2, but not experiment 2. However, given that incompletely-learned memories are seemingly more likely to undergo reconsolidation following reminder (Lee, 2009), the suggestion would be that it is the memory preservation effect in experiment 2, but not experiment 1.2, that involves memory reconsolidation processes. Without any reliable neural/biological marker of memory destabilization and reconsolidation (or indeed other memory process), it is impossible to determine the underlying mechanism of memory effects and whether they are similar across paradigms (Milton, Das, and Merlo, 2023).

Neither of our list learning reminder-dependent effects were observed in the failed replications of Hupbach et al (2007) conducted by Klingmuller et al (2017). We cannot provide a good explanation for this discrepancy and continue to agree that reminder-induced memory processes in human declarative memory remain poorly understood. Nevertheless, we do draw attention to potentially important procedural differences in our experiments that present challenges to any comparative interpretation. Our no-reminder control group was characterised by learning list 2 in a different context, in the presence of a novel experimenter and in the absence of any explicit reminder question. Klingmuller et al (2017) used an "experimenter-question" control group that re-exposed participants to the previous experimenter and included an explicit reminder question, but conducted in a non-training context. The use of this control group was reasonably motivated by previous observations that context reminder is sufficient to induce the asymmetric intrusion pattern (Hupbach et al., 2008), and Klingmuller et al (2017) directly addressed the potentially important impact of context familiarity. Nevertheless, the validity of the "experimenter-question" procedure as an effective control is at least as questionable as the replicability of the intrusion effect itself. Indeed, recent successful replications have used no-reminder controls similar to those employed in our present experiments (Capelo et al., 2019). Moreover, the absence of a no-interference control in Klingmuller et al (2017) makes it difficult to establish whether there were any interference effects on list 1 recall, in order to facilitate a comparison with our observation of reminder-induced protection from interference.

Given the prevailing uncertainty surrounding the effects of post-reminder interfering learning in human declarative memory settings, to which our current results only further contribute, we sought to establish whether alternative methods of memory interference might provide greater clarity. Using the same learning materials, albeit in a purely online setting, we observed that post-reminder playing of Tetris impaired test performance in the visual list learning, but not the foreign vocabulary learning, setting. This provides a partial conceptual replication of a series of studies showing the effect of Tetris as a visuospatial task to reduce intrusive recollection of trauma memories (James et al., 2015; Kessler et al., 2020), extending to an emotionally-neutral visual list learning setting. This pattern of genuine memory impairment is more clearly consistent with a disruption of memory reconsolidation, than are the previous observations of intrusions and protection from interference. Interestingly, in one previous study also demonstrating post-reminder memory impairment using the induction of emotional state, the effect appeared to be observed only in female participants (Pineyro, Ferrer Monti, Diaz, Bueno, Bustos, and Molina, 2018). Therefore, it is possible that our disproportionately-female participant pool may have influenced our results. An additional point to note is that commonly across our experiment 3.1 and previous studies using visuospatial interventions, there is no criterion of learning imposed, which might favour the engagement of reconsolidation by reminder (Lee, 2009). It is appealing, therefore, to conclude that in our visual list-learning paradigm, the reminder structure that we have employed does engage memory destabilisation and reconsolidation, which manifests in different ways depending upon the nature of the intervention and other factors that we do not fully understand. However, translation of our paradigm from in-person to online could equally have resulted in the reminder resulting in destabilisation only in the online setting. This reflects our continued poor understanding of the reminder conditions that are permissive for memory destabilisation (Jardine et al., 2022; Zhang, Haubrich, Bernabo, Finnie, and Nader, 2018).

The lack of effect of the visuospatial task on the foreign vocabulary memory may result from a number of different factors. First, the memory is inherently less visual in nature, meaning that a visuospatial task may interfere less than with the visual list memory. However, intervention task modality does not appear to be an important factor, at least in an analogue trauma setting (Hagenaars, Holmes, Klaassen, and Elzinga, 2017), and commonality of modality between the learned material and intervention task is no guarantee of impairment (e.g. Chalkia, Vanaken, Fonteyne, and Beckers, 2019). Moreover, while we implemented both a brief reminder and a full test as alternative reminders, it remains possible that neither were sufficient or optimal to cause memory destabilisation. Finally, we have to acknowledge that there has yet to be convincing evidence that reconsolidation-like effects can be observed in the foreign vocabulary learning setting (Finn and Roediger, 2011; Finn, Roediger, and Rosenzweig, 2012).

In summary, we have demonstrated that reminder of human declarative memory does render that memory susceptible to the impact of post-reminder behavioural intervention. However, the behavioural manifestation of that impact is not consistent across learning paradigms, behavioural interventions, or even within the same conceptual replication. Therefore, our understanding of reminder-induced memory processes in human declarative memory continues to be lacking. With the difficulty in replicating reconsolidation results in human fear memory settings (Chalkia et al., 2020; Stemerding et al., 2022), this supports the need for caution in the translational application of reminder/reconsolidation-based therapeutic strategies for PTSD and other psychiatric conditions.

CRediT authorship contribution statement

Kai Rong Tay: Conceptualization, Methodology, Formal analysis, Investigation, Data curation. **Francesca Bolt:** Conceptualization, Methodology, Investigation, Data curation. **Hei Ting Wong:** Conceptualization, Methodology, Investigation, Data curation. **Svetlina Vasileva:** Conceptualization, Methodology, Investigation, Data curation. **Jonathan Lee:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

Barak, S., & Goltseker, K. (2021). Targeting the Reconsolidation of Licit Drug Memories to Prevent Relapse: Focus on Alcohol and Nicotine. *International Journal of Molecular Sciences, 22*.

Ben Mamou, C., Gamache, K., & Nader, K. (2006). NMDA receptors are critical for unleashing consolidated auditory fear memories. *Nature Neuroscience, 9*, 1237–1239.

Brady, T. F., Konkle, T., Alvarez, G. A., & Oliva, A. (2008). Visual long-term memory has a massive storage capacity for object details. *Proceedings of the National Academy of Sciences of the United States of America, 105*, 14325–14329.

Capelo, A. M., Albuquerque, P. B., & Cadavid, S. (2019). Exploring the role of context on the existing evidence for reconsolidation of episodic memory. *Memory, 27*, 280–294.

Chalkia, A., Schroyens, N., Leng, L., Vanhasbroeck, N., Zenses, A. K., Van Oudenhove, L., & Beckers, T. (2020). No persistent attenuation of fear memories in humans: A registered replication of the reactivation-extinction effect. *Cortex, 129*, 496–509.

Chalkia, A., Vanaken, L., Fonteyne, R., & Beckers, T. (2019). Interfering with emotional processing resources upon associative threat memory reactivation does not affect memory retention. *Scientific Reports, 9*, 4175.

Crestani, A. P., Zacouteguy Boos, F., Haubrich, J., Ordoñez Sierra, R., Santana, F., Molina, J. M. D., Cassini, L. d. F., Alvares, L. d. O., & Quillfeldt, J. A. (2015). Memory reconsolidation may be disrupted by a distractor stimulus presented during reactivation, *Sci Rep. 5*, 13633.

De Oliveira Alvares, L., Crestani, A. P., Cassini, L. F., Haubrich, J., Santana, F., & Quillfeldt, J. A. (2013). Reactivation enables memory updating, precision-keeping and strengthening: Exploring the possible biological roles of reconsolidation. *Neuroscience, 244*, 42–48.

de Oliveira Alvares, L., Einarsson, E. O., Santana, F., Crestani, A. P., Haubrich, J., Cassini, L. F., … Quillfeldt, J. A. (2012). Periodically reactivated context memory retains its precision and dependence on the hippocampus. *Hippocampus, 22*, 1092–1095.

Finn, B., & Roediger, H. L., 3rd (2011). Enhancing retention through reconsolidation: Negative emotional arousal following retrieval enhances later recall. *Psychological Science, 22*, 781–786.

Finn, B., Roediger, H. L., 3rd, & Rosenzweig, E. (2012). Reconsolidation from negative emotional pictures: Is successful retrieval required? *Memory & Cognition, 40*, 1031–1045.

Forcato, C., Argibay, P. F., Pedreira, M. E., & Maldonado, H. (2009). Human reconsolidation does not always occur when a memory is retrieved: The relevance of the reminder structure. *Neurobiology of Learning and Memory, 91*, 50–57.

Forcato, C., Burgos, V. L., Argibay, P. F., Molina, V. A., Pedreira, M. E., & Maldonado, H. (2007). Reconsolidation of declarative memory in humans. *Learning & Memory, 14*, 295–303.

Forcato, C., Rodriguez, M. L., & Pedreira, M. E. (2011). Repeated labilization-reconsolidation processes strengthen declarative memory in humans. *PLoS One1, 6*, e23305.

Frenkel, L., Maldonado, H., & Delorenzi, A. (2005). Memory strengthening by a real-life episode during reconsolidation: An outcome of water deprivation via brain angiotensin II. *European Journal of Neuroscience, 22*, 1757–1766.

Gershman, S. J., Schapiro, A. C., Hupbach, A., & Norman, K. A. (2013). Neural context reinstatement predicts memory misattribution. *Journal of Neuroscience, 33*, 8590–8595.

Hagenaars, M. A., Holmes, E. A., Klaassen, F., & Elzinga, B. (2017). Tetris and Word games lead to fewer intrusive memories when applied several days after analogue trauma. *European Journal of Psychotraumatology, 8*, 1386959.

Halamish, V., & Bjork, R. A. (2011). When does testing enhance retention? A distribution-based interpretation of retrieval as a memory modifier. Journal of experimental psychology. *Learning, memory, and cognition, 37*, 801–812.

Hardwicke, T. E., Taqi, M., & Shanks, D. R. (2016). Postretrieval new learning does not reliably induce human memory updating via reconsolidation. *Proceedings of the National Academy of Sciences, 113*, 5206–5211.

Haubrich, J., & Nader, K. (2018). Memory Reconsolidation. *Curr Top. Behavioral Neuroscience, 37*, 151–176.

Hupbach, A., Gomez, R., Hardt, O., & Nadel, L. (2007). Reconsolidation of episodic memories: A subtle reminder triggers integration of new information. *Learning & Memory, 14*, 47–53.

Hupbach, A., Gomez, R., & Nadel, L. (2009). Episodic memory reconsolidation: Updating or source confusion? *Memory, 17*, 502–510.

Hupbach, A., Hardt, O., Gomez, R., & Nadel, L. (2008). The dynamics of memory: Context-dependent updating. *Learning & Memory, 15*, 574–579.

James, E. L., Bonsall, M. B., Hoppitt, L., Tunbridge, E. M., Geddes, J. R., Milton, A. L., & Holmes, E. A. (2015). Computer game play reduces intrusive memories of experimental trauma via reconsolidation-update mechanisms. *Psychological Science*.

Jardine, K. H., Huff, A. E., Wideman, C. E., McGraw, S. D., & Winters, B. D. (2022). The evidence for and against reactivation-induced memory updating in humans and nonhuman animals. *Neuroscience and Biobehavioral Reviews, 136*, Article 104598.

Karpicke, J. D., & Roediger, H. L., 3rd (2008). The critical importance of retrieval for learning. *Science, 319*, 966–968.

Kessler, H., Schmidt, A. C., James, E. L., Blackwell, S. E., von Rauchhaupt, M., Harren, K., … Holmes, E. A. (2020). Visuospatial computer game play after memory reminder delivered three days after a traumatic film reduces the number of intrusive memories of the experimental trauma. *Journal of Behavior Therapy and Experimental Psychiatry, 67*, Article 101454.

Klingmuller, A., Caplan, J. B., & Sommer, T. (2017). Intrusions in episodic memory: Reconsolidation or interference? *Learning & Memory, 24*, 216–224.

Lee, J. L. C. (2009). Reconsolidation: Maintaining memory relevance. *Trends in Neurosciences, 32*, 413–420.

Levy, D. A., Mika, R., Radzyminski, C., Ben-Zvi, S., & Tibon, R. (2018). Behavioral reconsolidation interference with episodic memory within-subjects is elusive. *Neurobiology of Learning and Memory, 150*, 75–83.

Luyten, L., & Beckers, T. (2017). A preregistered, direct replication attempt of the retrieval-extinction effect in cued fear conditioning in rats. *Neurobiology of Learning and Memory, 144*, 208–215.

Milton, A. L., Das, R. K., & Merlo, E. (2023). The challenge of memory destabilisation: From prediction error to prior expectations and biomarkers. *Brain Research Bulletin, 194*, 100–104.

Pineyro, M., Ferrer Monti, R. I., Diaz, H., Bueno, A. M., Bustos, S. G., & Molina, V. A. (2018). Positive emotional induction interferes with the reconsolidation of negative autobiographical memories, in women only. *Neurobiology of Learning and Memory, 155*, 508–518.

Potts, R., & Shanks, D. R. (2012). Can Testing Immunize Memories Against Interference? Journal of experimental psychology. *Learning*. memory, and cognition.

Roediger, H. L., & Karpicke, J. D. (2006). Test-enhanced learning: Taking memory tests improves long-term retention. *Psychological Science, 17*, 249–255.

Schroyens, N., Alfei, J. M., Schnell, A. E., Luyten, L., & Beckers, T. (2019). Limited replicability of drug-induced amnesia after contextual fear memory retrieval in rats. *Neurobiology of Learning and Memory, 166*, Article 107105.

Schwabe, L., & Wolf, O. T. (2009). New episodic learning interferes with the reconsolidation of autobiographical memories. *PLoS One1, 4*, e7519.

Scully, I. D., Napper, L. E., & Hupbach, A. (2016). *Does reactivation trigger episodic memory change? A meta-analysis*. Neurobiol Learn Mem.

Sederberg, P. B., Gershman, S. J., Polyn, S. M., & Norman, K. A. (2011). Human memory reconsolidation can be explained using the temporal context model. *Psychonomic Bulletin & Review, 18*, 455–468.

Sinclair, A. H., & Barense, M. D. (2019). Prediction Error and Memory Reactivation: How Incomplete Reminders Drive Reconsolidation. *Trends in Neurosciences, 42*, 727–739.

St Jacques, P. L., Olm, C., & Schacter, D. L. (2013). Neural mechanisms of reactivation-induced updating that enhance and distort memory. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 19671–19678.

Stemerding, L. E., Stibbe, D., van Ast, V. A., & Kindt, M. (2022). Demarcating the boundary conditions of memory reconsolidation: An unsuccessful replication. *Scientific Reports, 12*, 2285.

van Schie, K., van Veen, S. C., van den Hout, M. A., & Engelhard, I. M. (2017). Modification of episodic memories by novel learning: A failed replication study. *European Journal of Psychotraumatology, 8*, 1315291.

Wichert, S., Wolf, O. T., & Schwabe, L. (2013). Updating of episodic memories depends on the strength of new learning after memory reactivation. *Behavioral Neuroscience, 127*, 331–338.

Wideman, C. E., Jardine, K. H., & Winters, B. D. (2018). Involvement of classical neurotransmitter systems in memory reconsolidation: Focus on destabilization. *Neurobiology of Learning and Memory, 156*, 68–79.

Zhang, J. J., Haubrich, J., Bernabo, M., Finnie, P. S. B., & Nader, K. (2018). Limits on lability: Boundaries of reconsolidation and the relationship to metaplasticity. *Neurobiology of Learning and Memory, 154*, 78–86.