Time-dependent mnemonic vulnerability induced by new-learning

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22 **Abstract**

23 Reactivation renders consolidated memory labile again, and the ensuing temporary
 24 reconsolidation process is highly susceptible to mnemonic modification. Here, we
 25 show that memories in such an unstable state could be reprogrammed by sheer
 26 behavioral means, bypassing the need for pharmacological intervention. In two
 27 experiments using a “face-location association” paradigm in which participants
 28 experienced a “Learning – New-learning – Final-test” programme, we demonstrate
 29 that reactivated memory traces were robustly hampered when the new learning was
 30 strategically administered within a critical 20-minute time window. Using fMRI, we
 31 further advance our theoretical understanding that this lability can be mechanistically
 32 explained by the differential activation in the hippocampal-amygdala memory system
 33 implicated by the new-learning whereas the mnemonic intrusion caused by newly
 34 learned memories is efficaciously reconciled by the left inferior frontal gyrus. Our
 35 findings provide important implications for educational and clinical practices in
 36 devising effective strategies for memory integration.

37

38 **Keywords.** non-emotional declarative memory, reconsolidation, non-invasive
 39 manipulation, hippocampus, amygdala, IFG

40

41 **1 Introduction**

42 Memory recall is constructive in nature and the mere act of recalling a memory
43 renders it labile and highly susceptible to modification (Nader, Schafe et al. 2000, Lee,
44 Everitt et al. 2004, Lee, Di Ciano et al. 2005, Alberini and LeDoux 2013, Lee, Nader
45 et al. 2017, Scully, Napper et al. 2017). While emotional factors are known to exert
46 effects on reconsolidation of emotional declarative memories (Schwabe and Wolf
47 2009, Strange, Kroes et al. 2010, Chan and LaPaglia 2013), controversies still
48 surround reconsolidation theories on non-emotional declarative memories.
49 Empirically, post-retrieval manipulations gave rise to inconclusive patterns of results,
50 with some studies showing such manipulation can induce update (Hupbach, Gomez et
51 al. 2007, Hupbach, Gomez et al. 2009, Forcato, Rodriguez et al. 2010), forgetting
52 (Forcato, Burgos et al. 2007), extinction (Nader, Schafe et al. 2000, Schiller, Monfils
53 et al. 2010, Agren, Engman et al. 2012), or enhancement (Cocoz, Maldonado et al.
54 2011, Cocoz, Sandoval et al. 2013), whereas another set of studies revealing no
55 observable effect (Cammarota, Bevilaqua et al. 2004, Debiec, Doyère et al. 2006,
56 Hupbach, Hardt et al. 2008, Forcato, Argibay et al. 2009, Hupbach, Gomez et al. 2011,
57 Gershman, Schapiro et al. 2013). These previous studies indicate that manipulations
58 after reactivation would induce multiple, and at times conflicting, effects under
59 different conditions (Nader, Schafe et al. 2000, Pedreira, Perez-Cuesta et al. 2002,
60 Walker, Brakefield et al. 2003, Debiec, Doyère et al. 2006, Forcato, Argibay et al.
61 2009, Sederberg, Gershman et al. 2011, Sevenster, Beckers et al. 2012), it was thus
62 important to characterize these contributory factors. Specifically, reconsolidation is

63 known to be time-sensitive. The presence of this time-dependence in humans has been
64 coarsely derived from studies utilizing either one of the two extreme
65 reactivation-intervention intervals: either too short such that the reconsolidation was
66 still ongoing (e.g., 5 or 10 minutes, (Forcato, Burgos et al. 2007, Forcato, Argibay et
67 al. 2009, Schiller, Monfils et al. 2010, Agren, Engman et al. 2012)), or too long such
68 that the reconsolidation had concluded before the intervention began (e.g., 6 or 10
69 hours, (Forcato, Burgos et al. 2007, Schiller, Monfils et al. 2010, Agren, Engman et al.
70 2012)). Here we investigated the detailed temporal characteristics of reconsolidation
71 of declarative memory using gradient-like post-reactivation delays.

72 In light of the controversies surrounding theories on the reconstructive nature of
73 declarative memories, we evinced that human associative memories can be
74 exquisitely rendered labile by newly-acquired memories within a critical time-window.
75 Using a face-location association learning paradigm, human participants were made to
76 experience acquisition, test of associative-learning, reactivation, new-learning, and
77 final-test across three consecutive days. In a behavioral experiment (Fig. 1A, upper
78 panel), participants encoded 30 face-location associations on Day 1 (day1-Acquisition)
79 and following a 24-hour retention period, they were then divided into 5 groups and
80 asked to recall the associations they had acquired previously on day1
81 (day2-Reactivation). Importantly, the four different groups of participants received a
82 critical time-dependent new-learning manipulation (i.e., acquiring a new location
83 associated with the original 30 faces) whilst a fifth group acted as a control group and
84 did not receive any new-learning. The day2-New-learning served a critical

85 interventional purpose, aiming at interfering the originally acquired memories during
86 reconsolidation. On the third day (day3-Final-test), these participants were required to
87 recall again the face-location associations they had learned on day1-Acquisition. We
88 revealed the new-learning that occurred right after reactivation significantly
89 diminished the memory of the originally learned associations in a time-dependent
90 manner.

91 To elucidate the behavioral effects induced by the new-learning and the neural
92 underpinnings of the reconsolidation processes, we replicated the behavioral
93 experiment with a new group of participants performing a corresponding experiment
94 while their blood-oxygen-level-dependent (BOLD) activity was measured. We probed,
95 at a macro-anatomical level, in which regions might lie the influence of the
96 new-learning on the reconsolidation of non-emotional episodic memory (i.e., how
97 new-learning affected the originally learned memory) and how the intrusive effects
98 thereby induced by the newly-learned associations might manifest neurally. In this
99 fMRI experiment we included only one experimental group, which began their
100 new-learning immediately after reactivation on Day 2 (Fig. 1B-D). We employed
101 fMRI to unravel the mechanisms underlying the processes of integrating new
102 information into consolidated memories during reconsolidation.

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105 **Figure 1. Paradigm Overview.** (A) Experimental overview for behavioral and fMRI
 106 experiments. There were five and two groups in the two experiments, respectively.
 107 Each of the experiments, spanning across 3 daily sessions, consisted of four stages:
 108 Acquisition, Test of Associative-learning (Day 1), Reactivation, New-learning, Test of

109 New-learning (Day 2), and Final-test (Day 3). On Day 1, the subjects acquired a set of
 110 face-location associations (Acquisition). On Day 2, they were first asked to recall
 111 original associations (Reactivation) and were then divided into 4 experimental groups
 112 and one control group. After variable delays (i.e., 0', 20', 30', and 40'), they learned
 113 another set of associations of linking a new location to each of the original faces
 114 (New-learning). The control group did not receive any new learning. Finally, on Day
 115 3, these subjects were asked to recall the originally learned associations which they
 116 had acquired on Day 1 (Final-test). The participants in the fMRI experiment were
 117 scanned on Days 2 and 3. The cycle “×4” and “×2” denote the numbers of repetition
 118 in each of the tests. (B) Original learning (Acquisition) consisted of 30
 119 face-to-location associations. On each trial, a unique face was presented together with
 120 a location (out of five possible locations) on the screen for 4 s. The participants were
 121 instructed to memorize the associations. Their memories were then tested with Tests
 122 of Associative-learning. No feedback was given. (C) Importantly, using the identical
 123 procedure, on Day 2, 30 new associations were acquired *de novo* by the participants in
 124 the New-learning stage. (D) In Test of Associative-learning (AT), Reactivation (RE),
 125 Test of New-learning (NT), and Final-test (FT) stages, on each trial, the participants
 126 were required to indicate the correct location matched to each of the faces by pressing
 127 a 5-button keypad. In the Final-test, each response was classified into either a Correct
 128 response (blue discs), an Intrusive error (red discs), or a Non-intrusive error (grey
 129 discs). The colored discs, the face ID numbers and the location numbers (0-4) were
 130 not shown in the actual experiment. The order of face-presentation was randomized
 131 within and across participants in all stages.

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134 **2 Method**

135 The entire study consisted of one behavioral and one fMRI experiment. Each
 136 consisted of four experimental sessions across three days. The separation between

137 days was strictly controlled to be 24 hours (Fig. 1).

138 **2.1 Subjects**

139 151 participants took part in the behavioral experiment proper (four experimental
140 groups $n = 28$ each; control group $n = 39$) and 46 participants took part in the fMRI
141 experiment (experimental group $n = 18$; control group $n = 28$). All of them were
142 recruited from the East China Normal University (17 – 30 years old, mean =
143 22.05 ± 2.51 , SD, 26 males). All had normal or corrected-to-normal vision and reported
144 regular nocturnal sleep and no history of any neurological, psychiatric or endocrine
145 disorder. The participants received monetary compensation for their participation.
146 Written informed consents were obtained from all participants and the study was
147 approved by the University committee on Human Research Protection (UCHRP) at
148 East China Normal University. An additional 60 participants (37 and 23 for the
149 behavioral and fMRI experiments, respectively) were recruited but were not invited to
150 enter the subsequent sessions because their performance accuracy was below 40% in
151 the last round of the Test of Associative-learning on Day 1.

152 **2.2 Stimuli**

153 60 grayscale front-facing faces of neutral expression from unfamous volunteers
154 (30 males) were selected from CAS-PEAL-R1 database
155 (<http://www.jdl.ac.cn/peal/index.html>). These were divided into two sets of 30 faces
156 each (each set consisted of 15 males and 15 females). One set was used in the
157 behavioral and fMRI experiments, in which both day1-Acquisition and
158 day2-New-learning employing the same set of 30 faces (Fig. 1). The second set was

specifically used in the day2-New-learning phase for a control experiment wherein the 30 faces used in the new-learning were different from those used in the original learning session (Supplementary Fig. S1).

2.3 Behavioral experiments and analysis

The behavioral experiment investigated how the time interval between memory recall (i.e., reactivation) and interference (i.e., new-learning) affects memory reconsolidation. Four gradient-like time intervals between memory recall and interference were chosen: 0, 20 minutes, 30 minutes, and 40 minutes (four experimental groups). To obtain a reliable baseline for comparison, a control group was included in which no interference was applied (control group).

In a face-location association learning paradigm, the participants first familiarized themselves with the 30 faces on Day 1 (familiarization session) by viewing these faces passively. Each face was presented at the center of the screen for 3 s and separated by a jittered inter-trial interval of 2-4 s (mean = 3s). The whole set of 30 faces was presented three times in a randomized order.

Following the familiarization phase, the participants were then asked to memorize 30 face-location associations (day1-Acquisition; A), involving each face being paired with one of five location points on the screen. They were allowed 4 s to learn each pairing (Fig. 1B). Immediately after each acquisition of the 30 face-location pairings, a memory test ensued (Test of Associative-learning, AT, Fig. 1). On each test trial, the face cue and all five location points were presented together, and the participants were asked to indicate within 4 s which location disc was

181 originally paired with the face in the Acquisition stage by pressing the button
182 corresponding to the target location using an MRI-compatible keypad (see cartoon in
183 Fig. 1D). This Acquisition – Test of Associative-learning procedure was repeated four
184 times with the set of face-location associations presented in a new randomized order
185 in each cycle. The trials were separated by jittered inter-trial intervals of 3-7 s (mean
186 = 5s) and no feedback was given.

187 On Day 2, the participants were asked to recall their memory of the previously
188 learned face-location associations by identifying the target location that was
189 associated with a given face (day2-Reactivation; RE, Fig. 1). A New-learning
190 procedure was then administered aiming to interfere the processes of memory
191 reconsolidation. The participants were asked to learn to associate the
192 originally-learned faces with a new target location (i.e., learning new face-location
193 associations, Fig. 1C). This New-learning session consisted of four cycles of
194 New-learning (NL) and Test of New-learning (NT).

195 In order to pinpoint the temporal characteristics of interference on memory
196 reconsolidation, four temporal intervals, namely 0', 20', 30', and 40', between the
197 day2-Reactivation and New-learning were administered separately to the four
198 experimental groups. During these post-reactivation intervals, the participants listened
199 to light music without having to perform any task.

200 On Day 3, the participants recalled the face-location associations they had
201 acquired on Day 1 (day3-Final-test; FT), identifying the target locations that were
202 associated with given faces from Day 1.

203 A mixed 5 (between-group factor, four experimental conditions and control
204 condition) $\times$ 3 (within-group factor: Day1, Day2 and Day3) analysis of variance
205 (ANOVA) was applied on percentage correct data from the behavioral experiment.
206 Analogously, a mixed 2 (Group Exp. and Ctrl.) $\times$ 3 (Day1, Day2 and Day3) ANOVA
207 was applied on the data from the fMRI experiment.

208 Moreover, to account for inter-subject variability, the within-subjects correct rates
209 were normalized to obtain relative correct rates using the following equations,

210

$$\text{Relative Correct Rate}_{2-1} = \frac{\text{Correct Rate}_{\text{Day2-Reactivation}} - \text{Correct Rate}_{\text{Day1-Acquisition}}}{\text{Correct Rate}_{\text{Day1-Acquisition}}} \times 100\%$$

$$\text{Relative Correct Rate}_{3-2} = \frac{\text{Correct Rate}_{\text{Day3-Final}} - \text{Correct Rate}_{\text{Day2-Reactivation}}}{\text{Correct Rate}_{\text{Day2-Reactivation}}} \times 100\%$$

211

212 The within-subjects relative Correct Rate₂₋₁ reflects the memory decay after
213 Day1-Acquisition before Day2-Reactivation, whereas the relative Correct Rate₃₋₂
214 reflects the memory change due to the New-learning intervention.

215 **2.4 Classification of correct, intrusive and non-intrusive responses**

216 During the Final-test session, the participants were instructed to respond to the
217 target location as they learned in the acquisition on Day 1. Since the experimental
218 groups experienced new-learning on Day 2, there were three categories of responses
219 in the day3-Final-test. If the response was correctly matched with acquisition, it was a
220 correct hit. If it was incorrectly matched with the location they acquired in the new
221 learning on Day 2, it was classified as an intrusive error. Responses made to the other
222 three locations would be non-intrusive errors (Fig. 1D). We compared the difference

223 between the correct and the intrusive proportions among the groups. If the correct
224 rate/intrusive ratio was not significantly different between the experimental groups
225 and the control group, then we would infer that new learning did not cause any
226 significant effect. By contrast, if there were significant differences in the correct
227 rate/intrusion ratio between the groups, we would conclude that the new learning
228 might have disrupted the original-memory more severely in the experimental
229 group(s).

230 ***2.5 Control experiment: Effectiveness of content-similarity in memory intervention***

231 In declarative memories, content similarity shared between the acquisition and
232 new-learning material is a key factor for effective intervention as only similar new
233 materials were found to induce memory update, disruption or enhancement via
234 reconsolidation (Forcato, Burgos et al. 2007, Hupbach, Gomez et al. 2007, Cocozz,
235 Maldonado et al. 2011, Forcato, Rodriguez et al. 2011). We hypothesized that material
236 used in the post-reactivation intervention has to be similar enough to those used in the
237 acquisition to cause any discernible effect on the reconsolidation processes. To test
238 this prediction, we ran an additional control experiment in which we utilized new and
239 unencountered faces as the post-reactivation new-learning material (i.e., new faces to
240 be paired up with the original locations).

241 ***2.6 MRI acquisition and preprocessing***

242 Participants were scanned in a 3T MRI scanner (Trio Tim, Siemens) with a
243 quadrature volume head coil at the Shanghai Key Laboratory of Magnetic Resonance.
244 Thirty-three slices of functional MR images were acquired using a gradient EPI

sequence (EPI volumes per run = 192, FOV = 210×210 mm², matrix = 64×64, in-plane resolution = 3.75×3.75 mm², thickness = 4 mm, without gap, repetition time = 2 s, echo time = 30 ms, flip angle = 90°), covering the entire brain. A high-resolution structural image for each participant was also acquired using 3D MRI sequences for anatomical co-registration and normalization (FOV = 256×256 mm², matrix = 256×256, slice thickness=1 mm, without gap, repetition time = 2530 ms, echo time = 2.34 ms, flip angle = 7°).

SPM8 (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>) was used for data processing. For each participant, the functional images were realigned to correct for head movements. The structural image was co-registered with the mean EPI image, then segmented and generated normalized parameters to MNI space. Functional images were then normalized to the MNI space using these parameters, re-sampled to 2 mm isotropic voxel size and then spatially smoothed using an isotropic Gaussian kernel of 8 mm FWHM (full-width half-maximum). High-pass temporal filtering with a cut-off of 128 s was performed to remove low-frequency drifts.

2.7 fMRI data analysis

The fMRI experiment examined the neural correlates underlying the several aspects elicited by the new-learning interference on memory reconsolidation. The same face-location association learning paradigm as in the behavioral experiment was adopted. We implemented two Reactivation sessions on Day 2 and also two Final-test sessions on Day 3 to ensure a decent volume of data to be collected for the fMRI

analyses. Across the two sessions, we collected data for 60 test trials (i.e., two repetitions of the complete set of the 30 face-location pairs). Informed by the behavioral experiment that the memory reconsolidation processes were susceptible after a 0'-delay, we accordingly targeted at the 0' condition here. We included one control group, which received no new-learning after reactivation, for comparison. Trials were separated by jittered inter-trial intervals of 3-7 s (mean = 5s) and 18 4-s blank trials were included as baseline measurement. Each of the New-learning runs lasted for 10 min and each of the Reactivation/Final-test runs lasted for 6 min (Fig. 1C-D). The fMRI data for the day2-New-learning were not included for analysis.

Two sets of analyses (Day×Group model and Intrusion model) were carried out using a general linear model (**Error! Reference source not found.**). Statistical inference was based on a random effects approach, which comprised first-level analyses estimating contrasts of interest for each subject and second-level analyses for statistical inference at the group level with non-sphericity correction. For both models, in the first-level, each of the 60 test trials was modelled with a canonical hemodynamic response function time-locked to the trial onset as an event-related response with that trial's duration (mean duration = 2466 ms). The design matrix included six head motion regressors to remove the residual effects of head motion. The blank trials were not modelled. The estimated parameters values were used for the second-level group analysis.

The first model (Day×Group model) sought to identify brain areas that activated during reactivation and final-test. This allowed us to calculate the interaction effect

289 between the two factors for finding any evidence of episodic memory reconsolidation.

290 In the first-level analysis, the model included five regressors: $R_{(\text{Day2,Exp})}$, $R_{(\text{Day3,Exp})}$,
291 $R_{(\text{Day2,Ctrl})}$, $R_{(\text{Day3,Ctrl})}$, Misses, reflecting the responses of the experimental and control
292 groups in day2-Reactivation and day3-Final-test. For the group-level analysis, the
293 single-subjects contrast images for the 2 experimental conditions (i.e., “Day2/Day3”
294 trials, averaged across the two fMRI-runs) for each of the two groups were entered
295 into a mixed design ANOVA with “Day” as the within-subject variable and “Group”
296 as the between-groups variable. The random effects analysis consisted of an ANOVA
297 assessing the significance of Delta T -covariate at the group level. The statistical
298 threshold was set to $P\text{-FWE}=0.05$, whole brain corrected at peak level (cluster size
299 estimated at $P\text{-unc.} = 0.005$). With our *a priori* prediction, we performed small volume
300 correction (SVC) using a functional mask derived from subsequent memory effects as
301 the volume of interest (covering the hippocampus and the amygdala, (Kim 2011)).

302 The second model (Intrusion model) concerned responses during the final-test,
303 specifically investigating how new learning affected the original memory trace during
304 the reconsolidation process. The first-level model included three regressors obtained
305 from the day3-Final-test, reflecting the three types of the responses (correct, intrusive
306 or non-intrusive). Six motion regressors were also included. For the group-level
307 analysis, the single-subjects contrast images for the 3 experimental conditions (i.e.,
308 “correct/intrusive/non-intrusive” trials, averaged across the two fMRI-runs) were
309 entered into an ANOVA. The statistical threshold was set to $P\text{-FWE}=0.05$, whole
310 brain corrected at peak level (cluster size estimated at $P\text{-unc.} = 0.005$). The random

effects analysis consisted of a one-sample t-test assessing the significance of Delta T -covariate at the group level. Specifically, the “Intrusive > Non-intrusive” contrast revealed a cluster in the left inferior frontal gyrus. We accordingly extracted the beta estimates of the left IFG from each subject using Marsbar and correlated these beta estimates with the proportion of correct responses and the proportion of intrusive errors separately.

3 Results

3.1 Behavioral results: Main experiment

We revealed compelling evidence in support of the existence of reconsolidation. In the behavioral experiment, the Day $\times$ Group repeated measures ANOVA on percentage correct showed a strong “Day $\times$ Group” interaction effect ($F_{(8, 292)} = 7.26$, $P < 0.001$, Fig. 2A, Supplementary Table S1). We then ran two separate ANOVAs and found the group differences were only in the day3-Final-test, ($F_{(4, 146)} = 5.11$, $P = 0.002$, Fig. 2A, Supplementary Table S1) but not in day2-Reactivation ($F_{(4, 146)} = 0.39$, $P = 0.81$). In order to account for individual variances, we normalized the percentage correct data and re-ran ANOVAs on these synthetic, more sensitive indices. A 2 (correct rate₂₋₁; correct rate₃₋₂) $\times$ 5 (Group) repeated measures ANOVA equally showed a strong interaction between the factors ($F_{(4, 146)} = 6.00$, $P < 0.001$). Two separate ANOVAs showed that the interaction was driven by a main effect in relative correct rate₃₋₂ between Days 2 and 3, confirming that the significant between-group differences were specifically caused by new-learning (relative correct rate₃₋₂: $F_{(4, 146)} = 9.75$, $P < 0.001$, Fig. 2B right, Supplementary Table S2) but not before

333 new-learning (relative correct rate₂₋₁: $F_{(4, 146)} = 0.39$, $P = 0.81$, Fig. 2B left).

334 Motivated by previous findings on the time-dependence of post-retrieval
335 manipulations (Forcato, Burgos et al. 2007, Schiller, Monfils et al. 2010, Agren,
336 Engman et al. 2012, Chan and LaPaglia 2013), we then tested the hypothesis that
337 there would be a critical time-window for the observable post-reactivation
338 reconsolidation. As expected, the difference in the relative correct rates between Day
339 2 and Day 3 for Group 0' and 20' were significantly lower than other three groups (all
340 $P_s < 0.05$, LSD multi-comparison, Fig. 2B), indicating the influence of new-learning
341 was indeed highly time-dependent.

342 It has been reported that new-learning could produce an intrusive effect to our
343 memories by replacing the original memories in a specific retrograde manner
344 (Hupbach, Gomez et al. 2007, Hupbach, Gomez et al. 2009, Schiller, Monfils et al.
345 2010). In view of this, we tested for the intrusive effect in the current context. On
346 each trial, there were five location points; each of which could be a potential choice.
347 Operationally, for the experimental groups, at day3-Final-test, responses made to the
348 target location would be a hit, responses made to the newly-learned location would be
349 an intrusive error, whereas responses made to any of the other three locations would
350 be a non-intrusive error (see Methods). The intrusive proportion of Group 20' was
351 significantly higher than other three groups (all $P_s < 0.05$, Fig. 2C, Supplementary Fig.
352 S2, Supplementary Table S3), whereas these intrusive errors in the other three groups
353 did not differ. Interestingly, in Group 20', the intrusive proportion did not differ from
354 the correct rate, while in other three groups the correct rates were significantly higher

355 than the intrusive proportions (Supplementary Fig. S2, Supplementary Table S3),
 356 implying the new-learning might have caused differential effects on Group 0' and 20'.

357 We further analyzed these intrusive effects in all experimental groups.
 358 Interestingly, the quantity of intrusive errors in the 20' condition is significantly
 359 higher than those in the other conditions ($F_{(3,108)} = 5.08$, $P = 0.003$; LSD
 360 multi-comparison: $P_{(20'>0')} = 0.035^*$, $P_{(20'>30')} = 0.001^{**}$, $P_{(20'>40')} = 0.001^{**}$ vs. $P_{(0'>30')} = 0.21$, $P_{(0'>40')} = 0.23$, $P_{(30'>40')} = 0.96$), indicating the intrusive effects
 361 induced by new-learning following different post-reactivation delays are differential.
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365 **Figure 2. Behavioral results of both experiments.** (A) Memory performance plotted
 366 as a function of days in the behavioral experiment. Memory of the face-to-location
 367 associations diminished in all five groups gradually across days but a main effect of
 368 Group was found on Day 3 at the Final-test. (B) The reduction in memory in the
 369 behavioral experiment was plotted for relative correct rate₂₋₁ and relative correct

rate₃₋₂, respectively. There was no difference in Group for relative correct rate₂₋₁ but there was a significant interaction for the relative correct rate₃₋₂. Post-hoc tests confirmed that the memory for the Group 0' and 20' decreased far more drastically than Group 30', 40' and the control group. (C) The intrusive proportion of Group 20' was significantly larger than other groups. (D) Behavioral result in the fMRI experiment was consistent with that of the behavioral experiment. Both Group Exp. and Ctrl. performed similarly on Day 2. But the performance of the Group Exp., who had received post-reactivation New-learning on Day 2, diminished far more severely than Group Ctrl. at the Final-test. (E) Using a relative measure, in the fMRI experiment, there was no Group difference in the relative correct rate₂₋₁, but Group Exp. was significantly more impaired than Group Ctrl. in the relative correct rate₃₋₂. (F) The intrusive proportion of Group Exp. in the fMRI experiment (21.2%) was similar as Group 0' in the behavioral experiment (cf. leftmost bar in Fig. 2C). Error bar denotes standard error of the means. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

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3.2 Control experiment results: Effective manipulation requires high content-similarity between acquisition and intervention

In this control experiment, the new-face-learning caused no effect on reconsolidation. We ran a 3×2 repeated measures ANOVA (Day $\times$ Group) on percentage correct and found neither a group main effect nor an interaction effect (group main effect: $F_{(1,2)} = 1.49$, $p = 0.24$; interaction: $F_{(2,2)} = 1.29$, $p = 0.29$; Supplementary Fig. S1). We conducted the post-hoc tests regardless and confirmed there were no group differences in day2-Reactivation ($t_{(1,20)} = 0.47$, $p = 0.65$) or day3-Final-test ($t_{(1,20)} = -0.22$, $p = 0.82$), nor in the relative correct rate₃₋₂ between Days 2 and 3 ($t_{(1,20)} = -1.36$, $p = 0.19$). These indicate that new-learning using “new faces” was ineffective in causing interference in the memory traces during

396 reconsolidation.

397 **3.3 fMRI experiment results**

398 We have thus far established in the behavioral experiment that new-learning
 399 following reactivation did intrude into the already encoded, yet labile memories, and
 400 produce overt changes in terms of memory behavior. We then tap into the rather
 401 complicated and unresolved mechanisms of reconsolidation by means of functional
 402 imaging. We replicated these behavioral patterns in the fMRI experiment with a new
 403 group of participants. A 2×2 repeated measures ANOVA (Day×Group) showed an
 404 interaction effect ($F_{(2, 88)} = 6.86, P = 0.002$, Fig. 2D). The performance for the
 405 experimental group was significantly lower than that of control group in the relative
 406 correct rate₃₋₂ ($t_{(44)} = -3.65, P < 0.001$, Fig. 2E right) but not in the relative correct
 407 rates₂₋₁ ($t_{(44)} = 0.18, P = 0.860$, Fig. 2E left).

408 To look into the neural correlates, we ran a “Day×Group” model to test for the
 409 interaction between Day and Group to look for the effects of new-learning on original
 410 memory. Specifically, the interaction term ($R_{\text{Day2,Exp}} - R_{\text{Day3,Exp}}$) vs. ($R_{\text{Day2,Ctrl}} - R_{\text{Day3,Ctrl}}$)
 411 revealed activation of left hippocampus and right amygdala (Fig. 3). Both regions
 412 yielded significant activation (hippocampus: peak $P\text{-svc} = 0.049$; amygdala: peak
 413 $P\text{-svc} = 0.037$) with small volume correction (SVC) (volume-of-interest obtained
 414 from a subsequent memory effects contrast: remembered vs. forgotten)(Kim 2011).
 415 Notably, the amygdala has been known to be related to emotional processes especially
 416 by those that are involved in fear and threat memory reconsolidation (Agren, Engman
 417 et al. 2012, Schiller, Kanen et al. 2013). However, in the present setting, considering

our paradigm did not contain any emotional factors, the right amygdala was implicated regardless.

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Table 1. Summary of all 1st-/2nd-level analyses and contrasts for both models.

Models	First-level	Second-level	
	<i>Regressors</i>	<i>Contrasts</i>	<i>Search Volume</i>
Day×Group	R _{Day2,Exp} , R _{Day3,Exp} , R _{Day2,Ctrl} ,	(R _{Day2,Exp} -R _{Day3,Exp})	> SVC (hippocampus and amygdala)
	R _{Day3,Ctrl} , Misses	(R _{Day2,Ctrl} -R _{Day3,Ctrl})	
Intrusion	Correct, Intrusive,	Intrusive > Non-intrusive	Whole-brain; SVC (left IFG)
	Non-intrusive (including Misses)		

R refers to trials in which subjects made a response on day2-Reactivation and day3-Final-test, irrespective of being correct or incorrect; Misses refer to trials of no response. Corrects, Intrusive and Non-intrusive errors classification are illustrated in Fig. 1D.

428

429

430 **Figure 3. Neural correlates associated with the impact of new-learning on**
 431 **reconsolidation.** Hippocampal and amygdala are differentially activated at the
 432 Final-test following New-learning administered during reconsolidation on Day 2, as
 433 given by the interaction term: $(R_{\text{Day2, Exp}} - R_{\text{Day3, Exp}}) > (R_{\text{Day2, Ctrl}} - R_{\text{Day3, Ctrl}})$; $P\text{-SVC} <$
 434 0.05.

435

436 In a separate model (Intrusion model), the contrast “Intrusive Non-intrusive
 437 errors” revealed activation of the left inferior frontal gyrus (IFG, Fig. 4). This
 438 indicated the post-reactivation new-learning was associated with activation in the
 439 inferior frontal area, which has long been implicated in resolving interference between
 440 competing mnemonic representations of the originally learned and newly acquired
 441 associations (Badre, Poldrack et al. 2005). For consistency, we also performed SVC
 442 for the IFG using a functional mask defined in a previous study (mid-ventrolateral
 443 PFC, post-retrieval selection) (Badre, Poldrack et al. 2005) and confirmed the results
 444 (peak $P\text{-svc} = 0.010$).

445 To elucidate the functional significance of the inferior frontal activation in

446 relation to the behavioral results, we extracted the beta estimates of BOLD signal
 447 from the left IFG cluster and correlated these individual beta estimates with subjects'
 448 percentage correct and intrusive proportion respectively. The individual beta estimates
 449 showed a significant positive correlation with the percentage correct rates ($r = 0.48$, P
 450 $= 0.045$, Fig. 4 left panel), whereas the beta estimates showed a negative correlation
 451 with the subjects' intrusive proportion ($r = -0.45$, $P = 0.060$, Fig. 4 right panel). We
 452 interpret these pattern of results as that the IFG is involved in mediating the
 453 recollection bias towards the originally learned information. The more strongly the
 454 inferior frontal cortex is activated, the successful the participant would be in
 455 discriminating the respective memory traces associated with the original acquisition
 456 and new-learning, whereas a weaker inferior frontal involvement signifying a lower
 457 ability in dealing with the competition between mnemonic representations of the
 458 initially-learned and newly-acquired associations.

459

460

461 **Figure 4. Engagement of IFG by new-learning intrusion.** Left IFG activation

measured on the Final-test reflects individuals' variability in guarding against memory intrusion imposed by New-learning during reconsolidation on Day 2. The left inferior frontal gyrus is more activated by intrusive errors than by non-intrusive errors during Final-test ($P < 0.05$). This difference in neural activation mediated the behavioral performance. Activation in the left IFG across participants is correlated positively with the percentage correct ($P = 0.045$, left), but is correlated in a negative trend with the number of intrusive errors ($P = 0.060$, right). Such IFG activation is however not correlated with the number of non-intrusive errors ($P > 0.5$, not shown). This result shows that post-reactivation new-learning manipulates memory by affecting reconsolidation on day 2, with the intrusion-effects being observed on day 3 in the Final-test. Triangles on the scatterplots represent individual subjects. The central line is the best linear fit with 90% confidence interval.

4 Discussion

In light of the previous studies which failed to observe the reconsolidation process in humans and non-human animals (Cammarota, Bevilacqua et al. 2004, Debiec, Doyère et al. 2006, Forcato, Argibay et al. 2009), we deduced several factors which might be instrumental for the reconsolidation processes at play. In declarative memories, content similarity shared between the acquisition and new-learning material is a key factor for effective intervention as only similar new materials were found to induce memory update, disruption or enhancement via reconsolidation (Forcato, Burgos et al. 2007, Hupbach, Gomez et al. 2007, Cocoz, Maldonado et al. 2011, Forcato, Rodriguez et al. 2011). Based on the results of the control experiment, we ascertain that the new-learning was most effective in affecting reconsolidation when "same faces" were employed. We thus assert that reconsolidation could be

487 disrupted by post-reactivation new-learning *if and only if* the new material was similar
 488 enough to those involved in the acquisition, establishing content similarity in the
 489 associative memory traces between acquisition and new-learning to be a determinant
 490 factor. If the new-face-learning was distinct from the reactivated memory traces then
 491 these new-face-learning might have induced a different set of consolidation processes
 492 independently of the targeted reactivation.

493 In the rodents, any intervention disrupting memory reconsolidation is only
 494 effective when it is administered shortly after reactivation (Nader, Schafe et al. 2000,
 495 Debiec, LeDoux et al. 2002, Pedreira, Perez-Cuesta et al. 2002, Debiec and Ledoux
 496 2004), suggesting that reconsolidation is a highly time-dependent phenomenon. In the
 497 humans, there has not been a consensus on the precise interval for this mnemonic
 498 fragility (Forcato, Burgos et al. 2007, Schiller, Monfils et al. 2010, Agren, Engman et
 499 al. 2012). Our current study incorporated a range of gradient-like post-reactivation
 500 delays. The New-learning administered within 20 minutes caused retrograde amnesia,
 501 whereas delays longer than that elicited no effect. Our results thus provide a qualifier
 502 on defining the critical time-window for post-reactivation manipulation to be effective
 503 for inducing forgetting: immediately after reactivation when memory is being updated.
 504 When the interval was long and beyond the susceptible period, the reactivated
 505 memories would become stable again and immune to any new-learning, thus no effect
 506 would be observed. This conclusion is further verified by the analyses of the intrusive
 507 effect reported in Fig. 2C, which illustrate that the differential intrusive effects
 508 induced by new-learning following different post-reactivation delays.

509 Our fMRI findings demonstrate how the memory systems might have acted
510 interactively in declarative memory reconsolidation. It is known that memory
511 reactivation will render consolidated memory (hippocampus-independent) to be
512 hippocampus-dependent again (Debiec, LeDoux et al. 2002, Kelly, Laroche et al.
513 2003, Lee, Everitt et al. 2004). Our fMRI results reveal that memory processes during
514 reconsolidation are hippocampus-dependent, strengthening the view that the
515 hippocampal and amygdala involvement change with the passage of time during
516 reconsolidation (Agren, Engman et al. 2012, Schwabe, Nader et al. 2012). When the
517 post-reactivation manipulation requiring the hippocampus (and amygdala) to process
518 new but similar information during active reconsolidation, the originally acquired
519 memories would be affected by disruption or intrusion.

520 In contrast to previous studies (Nader, Schafe et al. 2000, Debiec and Ledoux
521 2004, Lee, Di Ciano et al. 2005), the amygdala activation was presently observed in
522 the absence of emotional input or incentive factors (neutral faces □ location
523 association). We proposed two possible explanations for this: First, the faces encoded
524 by the participants might inherently carry emotional valence and collaterally engaged
525 the amygdala. However, an alternative, more nascent, account is that the amygdala
526 has a seat during declarative memories reconsolidation, irrespective of emotion
527 aspects, acting in concert with the hippocampus. We are in favor of the latter account
528 especially our results align with some recent causal evidence that the human
529 amygdala possesses a general capacity to endogenously initiate memory prioritization
530 processes of declarative memories without eliciting any subjective emotional response

(Inman, Manns et al. 2018), establishing the amygdala as an overarching operator of downstream memory processes.

The activation in the left inferior frontal gyrus was differentially increased by intrusive events, suggesting that left IFG is involved in discriminating the originally learned and newly-learned memories and deciding which memories should be reactivated according to the cue (Zhang, Feng et al. 2004, Badre, Poldrack et al. 2005, Moss, Abdallah et al. 2005, St Jacques, Olm et al. 2013). Due to the high similarity between the originally learned and newly learned memories, the participants have to recollect the episodes in greater detail to overcome the competition and meet the goal in recalling the relevant, correct memories among competitive sources. In line with the view that the left ventral PFC mediates post-retrieval selection during source recollection and decision (Badre, Poldrack et al. 2005, Badre and Wagner 2007), our findings of increased left IFG activation characterize this region as a target area for manipulating memory retrieval especially during reconsolidation. The individual difference in left IFG activation among participants further serves as an indicator of individual's ability in reconciling the mnemonic intrusion during memory reconsolidation.

5 Conclusion

Overall, we reveal three neuro-behavioral features in declarative memory reconsolidation in humans. The results provided insights into the mechanisms of episodic memory reconsolidation, suggesting that reactivation can indeed effectively trigger reconsolidation with several qualifiers. First, new-learning is effective only

553 when sharing common components with initial learning (acquisition). Second, we
 554 establish the existence of a critical time-window for reconsolidation, defining it to be
 555 20 minutes. Third, we show the involvement of the hippocampus and amygdala in
 556 integrating newly-formed memories during reconsolidation, and with the IFG
 557 resolving the mnemonic competition caused by the intrusion by newly-formed
 558 memories. From a translational perspective, the present findings support the
 559 possibility that non-invasive manipulation may one day make drug therapy obsolete
 560 and carry important implications for educational and clinical practices in devising
 561 learning strategies.

562

563 **Supplementary information** containing 2 figures and 3 tables is included.

564

565 **Author Contributions**

566 All authors contributed to the study design. F. S., J. W., and Y. C. conducted the
567 behavioral experiment. F. S. and J. L. performed the fMRI experiment. F. S., Y. K., Z.
568 W., H. W. and S. C. K. analyzed the data. F. S., Z. W., H. W. and S. C. K. wrote and
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570

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583

584 **Declaration of Conflicting Interest**

585 The author(s) declared that there were no conflicts of interest with respect to the
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587

588 **Open Practices Statement**

589 The data that support the findings of this study are available from the corresponding

590 author on request.

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