A retrieval-counterconditioning procedure diminishes reinstatement of appetitive memories in humans

Rani Gera[1,2,3], Segev Barak[1,2,4*] and Tom Schonberg[1,3,4*]
[1]Sagol School of Neuroscience, [2]School of Psychological Sciences, [3]Department of Neurobiology, Tel Aviv University, 69978 Tel Aviv, Israel
[4]Tom Schonberg and Segev Barak contributed equally to this work

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*Corresponding Authors:
Tom Schonberg
Faculty of Life Sciences, Department of Neurobiology and The Sagol School of Neuroscience
Tel Aviv University
Tel Aviv 69978, Israel
Tel. +972-3-6406808
Fax +972-3-6406907
schonberg@post.tau.ac.il

Segev Barak
School of Psychological Sciences and The Sagol School of Neuroscience
Tel Aviv University
Tel Aviv 69978, Israel
Tel. +972-3-6408969
Fax +972-3-6409547
barakseg@post.tau.ac.il

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Conflict of Interest

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Abstract

Appetitive memories play a crucial role in learning and behavior. Despite their adaptive function, under certain circumstances they can take a maladaptive form and play a vital part in addiction and other psychopathologies. In recent years, scientific research demonstrated the ability of memories to be modified following their reactivation through memory retrieval, in a process termed memory reconsolidation. Several non-pharmacological behavioral manipulations yielded mixed results in their capacity to alter maladaptive memories. Here, we tested the efficacy of aversive counterconditioning to alter appetitive memories in humans, when given following memory retrieval. We constructed a three-day experiment: On Day 1, we conditioned computerized contexts with monetary gain. On Day 2, we retrieved the relevant memory for half of the participants (Retrieval group). Then, all participants underwent counterconditioning, where the contexts were re-associated with monetary loss. On Day 3, to reinstate responses originated on Day 1, participants gained money, but without the presentation of any context. We used a binary choice task to measure changes in context preference following each manipulation. Appetitive memories were successfully formed through conditioning, then counterconditioned, and later reinstated. We observed a reduced reinstatement of the original appetitive memory when counterconditioning was induced following memory retrieval. We provide here a novel human paradigm that models several memory processes, and demonstrate memory attenuation when counterconditioned after its retrieval. This paradigm can be used to study complex appetitive memory dynamics, e.g., memory reconsolidation, and their underlying brain mechanisms.

Significance Statement

Extinguished appetitive memories recover under certain circumstances, which may have clinical implications, such as relapse in drug addiction. In the process termed reconsolidation, memories can be altered following their retrieval. Here, we established a novel behavioral procedure in healthy human participants, where we employed counterconditioning following memory retrieval to diminish memory recovery. We significantly reduced the recovery of related choices in the retrieval group compared to a control group that did not undergo retrieval. This paradigm can be used to study complex appetitive memory dynamics and their underlying brain mechanisms.

Keywords: Memory, Reconsolidation, Reinstatement, Counterconditioning, Appetitive conditioning

Introduction

Appetitive associative memories play a crucial role in motivation, learning, behavior and decision-making (Cardinal et al., 2002). Over the last two decades, it has been demonstrated that associative memories can be modified when manipulated during the process of 'memory reconsolidation' (for review see Lee et al., 2017). In this process, reactivation of consolidated memories via their retrieval initiates a temporary labile state that lasts a few hours ("reconsolidation window"), during which the memories are prone for modification before their re-stabilization (Nader and Hardt, 2009; Dudai, 2012).

Interference with the reconsolidation process can potentially disrupt or update the original memory, consequently preventing its expression, and thus holds significant clinical implications (Beckers and Kindt, 2017). Despite the substantial clinical potential, only a few studies targeted the reconsolidation of appetitive memories in humans. Several of these studies employed pharmacological interventions during reconsolidation of appetitive memories (Corlett et al., 2013; Saladin et al., 2013; Xue et al., 2017), but a pharmacological approach may be limited due to its potential side effects.

A few other studies employed behavioral manipulations during reconsolidation of appetitive memories (Xue et al., 2012; Das et al., 2015b; Germeroth et al., 2017), all in drug addicts or heavy alcohol abusers, where the target memory pre-existed prior to the study. However, a basic-research paradigm of these memory processes in healthy human individuals is yet to be developed. Recently, Goltseker et al. (2017) developed a novel behavioral paradigm in mice and demonstrated that administering aversive counterconditioning training following the retrieval of cocaine-associated memories abolished the reinstatement of cocaine seeking in mice. Here, we aimed to translate this novel retrieval-counterconditioning animal model to a new human paradigm that alters appetitive memories in healthy participants. A controlled

laboratory task, in which the target memory is formed under fully controlled settings, is vital for understanding the fundamental mechanisms of memory dynamics.

We designed a behavioral procedure consisting of three stages, during which appetitive memories were formed in the laboratory, then counterconditioned and finally reinstated. Aiming to disrupt the reconsolidation of these memories by behavioral interference, we reactivated them prior to their counterconditioning for one group but not the other, by a brief memory retrieval. We hypothesized that such treatment will reduce or eliminate the reinstatement of these memories only in the retrieval group.

Materials and Methods

Participants. Ninety-six (63 females) healthy participants participated in the experiment. Our target sample size was n=50 valid participants that demonstrated adequate learning based on certain criteria (see Experimental Design and Statistical Analysis below for details). We aimed to obtain n=25 in each of the 2 groups: Retrieval and No-Retrieval. The 50 valid participants (age range 18-39, mean=24.82, sd=4.52) included 35 females. All participants had normal or corrected to normal vision and gave their informed consent prior to participation in the experiment in return for monetary compensation (40 NIS =~ $12 USD per hour). Participants were informed that apart from the hourly fee, they may gain or lose an additional monetary bonus. They were guaranteed that even if their losses would exceed their gains, as calculated from the beginning of the experiment (beginning of the first day), they would still receive as a minimum the promised hourly rate. Therefore, their total compensation in each point could not be less than the hourly accumulated payment. The study was approved by the ethics committee of Tel Aviv University. The experiment was performed in accordance with relevant guidelines and regulations. Four participants were excluded due to software failures, and eight due to

incompletion of the experiment. Thus, a total of n=84 were valid participants out of which n=50 (n=25 in each group) qualified our experimental exclusion criteria.

Apparatus. Tasks were presented on an iMac monitor (21.5") with 1920*1080 resolution and 60Hz refresh rate. The experiment was programmed and run in MATLAB R2014b (MathWorks; RRID:SCR_001622), using the Psychtoolbox-3 (Brainard, 1997; Kleiner et al., 2007; RRID:SCR_002881). Participants sat in one of two designated testing rooms and wore noise cancelling headphones. Participants in the No-Retrieval group, performed the first fifteen minutes of the second day in a third room with similar settings, located in an adjacent building.

Procedure

The experiment consisted of three stages (Conditioning, Counterconditioning, Reinstatement), across three consecutive days. Participants were randomly assigned to the Retrieval and No-Retrieval groups. The overall workflow of experimental procedures is illustrated in Figure 1A. Briefly, on Day 1 we first measured participants' baseline liking toward different stimuli and assembled the CSs accordingly. Subsequently, participants underwent appetitive conditioning. On Day 2, after retrieving the memory only for the Retrieval group, participants from both groups underwent counterconditioning. On Day 3 we aimed to reinstate the memory that was formed through conditioning. Preferences, as well as liking ratings, were measured following the different stages of the task and probed changes in preference and liking toward the CSs. We used computerized simulated houses as the CSs, and monetary gain and loss as appetitive and aversive UCSs, respectively.

DAY 1

Baseline fractals liking ratings: Upon arrival, participants rated their liking towards eighteen fractal art images (see https://osf.io/48uca/ for a sources list) on a visual analogue scale (VAS)

ranging from 0 to 10 (Liking rating baseline) (see Figure 1B). The fractal collection was assembled of three sets of six fractals each, considerably distinctive in color (red, green and blue). Fractal presentation order was randomized and the task was self-paced.

To avoid a baseline color preference effect in subsequent tasks, we implemented the following algorithm (see Figure 2): For each participant, the scores of all stimuli rated were averaged. The three stimuli of each color (red, green and blue) that were the closest to the mean of all ratings were chosen to be used as the nine CSs (6 CS- and 3 CS+). Then, the average score for each CS color set was calculated. The six stimuli that belonged to the colors with the highest and lowest averages were used as CS-, and the three stimuli of the color with the intermediate average assembled the CS+. This method maximized the probability that the CS+ color is not the most liked or disliked color by each participant. The use of color groups was designed to allow participants to verbalize a rule, and thus increase contingency awareness, which has been shown to promote the occurrence and magnitude of conditioning (for example see Clark and Squire, 1998; Field and Duka, 2001; Hogarth and Duka, 2006).

Conditioning*:* Participants were instructed that they will participate in a computerized simulated tour, during which they will enter different houses (see Figure 1C). A total of nine houses were designed with the same floor and were distinguished by their wallpaper background. Each of the nine fractals assigned to assemble the CSs according to the subjective liking rating baseline served as the background of one house. Participants were instructed that in some of the houses they will receive money whereas in other houses, money will be taken away from them.

The task consisted of 20 blocks. On each block, participants visited each house once in a randomized order, spending 9 seconds inside a house on each visit. A third of all houses (=three houses), members of the same color set, were assigned as CS+ and paired with monetary gain. On each visit of a paired house, a monetary reward (of 0.18 NIS, 5 cents on

average) was delivered twice within the 9-second entry, indicated by a short animation of coins and the sum gained, popping up, accompanied by a winning casino-like sound (See Figure 1C). In the other houses (CS-), no monetary gain nor loss was delivered.

We implemented an instrumental gaming-like sequence assignment, scheduled to occur once in each house visit. Participants were instructed that sometimes, while they will be inside a house, an assignment will appear, where they will be requested to enter a sequence of letters as fast as possible (see Figure 1C) within 1.5 seconds. They were informed that this sequence assignment may lead to “winning” or “losing" and that the faster they will press the sequence, the more money they will win or the less money they will lose. Alternatively, this sequence assignment may be “neutral”, resulting in no monetary outcome regardless of their performance. Gains and losses ranged between 0 to 0.20 NIS (~$0-$0.06 USD), determined by the relative duration until the correct sequence was entered. In reality, during the conditioning stage all the assignments in the paired houses (CS+) were winning and all the assignments in the unpaired houses (CS-) were neutral. These sequence-pressing assignments were designed to increase participants’ engagement and enhance conditioning efficacy with an additional appetitive component that is paired with the paired houses (CS+). The total duration of the conditioning stage was ~32 minutes including transition between houses (excluding ~4 minutes instructions and task demonstration).

To facilitate learning we used a constant presentation order within each 9-second visit of each paired houses: spontaneous gain, sequence task, and another spontaneous gain. To improve the realistic narrative of the simulated tour, a “neighborhood” screen appeared once before the tour started, presenting the different houses with roads connecting between them (see Figure 1C). Additionally, the transition between houses was indicated by the presentation of the next house to which the participant was about to enter, simulated from the outside, with a path leading to it and a door (Figure 1C). To open the door participants were required to press

a designated keyboard button. Finally, the instructions were designed to convey a story-like description, e.g., we named the neighborhood and then used its name throughout all stages of the experiment when referring to the houses.

Participants were not informed of the true goal of the task. Apart from encouraging them to respond as fast as they could in the *sequences assignments*, we did not explicitly direct them to notice, identify or act in any particular manner.

Binary choice probe 1: After conditioning, participants performed a binary choice probe (preference test). This task served to measure preferences toward the paired houses (CS+) following conditioning. In this task, participants were presented with two houses on each trial and were instructed to choose the house they preferred to enter (see Figure 1D). Participants had 2 seconds to make each choice. They were told that on the last day of the experiment, one of the trials will be randomly chosen and that they will enter the house they chose on that particular trial and will get to spend a few minutes inside that house. We encouraged participants to treat every pair as if it was the one that will be chosen at the end of the experiment and thus act accordingly. The probe phase included two blocks. On each block, each one of the three CS+ was compared with all six CS-, constituting eighteen comparisons (3*6). To avoid a mere-exposure effect (Zajonc, 1968) additional nine comparisons (3*3), each consisting of two different CS-, one from each of the two color-sets assigned as the CS-, were presented to participants on each block. Thus, each CS appeared the exact same number of times. Trial order was randomized within each block.

In order to minimize the influence of working memory recruited during Conditioning on choices in this task, we included a faces liking ratings task between Conditioning and Binary choice probe. The structure of the task was similar to the Fractals liking ratings, except that the participants were asked to rank 60 unfamiliar faces (Yovel and Kanwisher, 2004).

Fractals liking ratings test 1: This test was identical to the Baseline fractals liking ratings and was used to assess changes in liking toward the stimuli that assembled the paired houses compared to the stimuli that assembled the unpaired houses following conditioning.

DAY 2

Memory Retrieval: Upon arrival, the Retrieval group participants performed a short automated simulated tour in the same neighborhood they toured on Day 1. The task included two visits to each of the three paired houses (CS+). The visits were similar to Day 1, except that no money was earned during these visits. Prediction error was suggested to be vital to induce memory reconsolidation (Pedreira, 2004; Lee, 2008; Sevenster et al., 2013), therefore the instructions, as well as the presentation of the neighborhood screen, were equivalent to the respective components of the Day 1 Conditioning stage. This was meant to increase expectancy violation by inducing participants' expectations for an equivalent task as in Day 1. The total duration of the retrieval task was ~1.5 minutes.

Following the completion of the Memory retrieval task by the Retrieval group, participants watched a short nature video (~12 minutes including instructions) to provide a temporal separation between memory retrieval and subsequent counterconditioning. This was done to induce destabilization of the existing memory (Beckers and Kindt, 2017). While watching the video, participants were asked to answer a total of 15 multiple-choice questions regarding its content. The questions were presented on the screen at a predetermined timing (every 41.3 seconds on average, SD=23.7) while the video was playing. Participants were given 10 seconds to read and answer each question. This task was fixed in duration and ensured constant working memory engagement. Participants in the No-Retrieval group performed the movie part upon arrival without the memory retrieval phase. They performed this part at a nearby building with a different experimenter to avoid unintentional memory reactivation via

physical context (Hupbach et al., 2008). Upon completion of the movie, they were instructed to go to the original testing room in the laboratory to continue the experiment.

Counterconditioning: The counterconditioning stage on Day 2 was similar to the Conditioning stage in Day 1, except that the previously paired houses (CS+) were paired with monetary loss rather than gain, with equivalent amount and contingency as in Day 1. Consistently, all the sequence assignments in the paired houses led to losses. The assignments in the unpaired houses remained neutral. We anticipated that due to loss aversion (Tversky and Kahneman, 1992), counterconditioning will be more potent compared to conditioning. Therefore, we set the given time in the assignments (1.5 second) to be sufficient for the majority of participants to win a greater sum of money on Day 1 than they lost on Day 2. Consequently, the sequence assignments led to unequal gains/losses between Day 1 and 2. The total duration of the counterconditioning stage was equivalent to the conditioning stage (~32 minutes).

Binary choice probe 2: This stage was identical to the previous Binary Choice Probe. It was used to confirm that counterconditioning led to a reduction in preference toward the paired houses.

Fractals liking ratings test 2: This test was identical to the previous Fractals liking ratings and used to assess changes in liking toward the stimuli that assembled the paired houses compared to the stimuli that assembled the unpaired houses following counterconditioning.

DAY 3

Reinstatement: Upon their arrival to the laboratory on Day 3, participants from both groups performed a reinstatement task by re-exposure to the UCS (Bouton, 2002). This was designed to reinstate the preference induced by the original Day 1 appetitive associations. Participants were instructed that they will take a short simulated tour, similar to the preceding days, except that the simulated houses will appear with no background wallpaper (i.e. without the fractals). During the task, participants entered 6 no-background houses, all yielding monetary gain,

similar to the paired houses on Day 1. Consistently, all sequence assignments led to wins. The total duration of the reinstatement task was ~1.5 minutes.

Binary choice probe 3: This stage was identical to the previous Binary choice probes. It was used to assess whether and to what extent, the reinstatement procedure recovered (i.e., increased) the preference toward the paired houses.

Fractals liking ratings test 3: This test was identical to the previous Fractals liking ratings. It was used to assess changes in liking toward the stimuli that assembled the paired houses compared to the stimuli that assembled the unpaired houses following the reinstatement procedure.

POST EXPERIMENT TASKS

Loss aversion questionnaire: We asked participants to fill in a loss aversion questionnaire to test for differences between groups and if it would have affected the subjective intensity of the counterconditioning. We used a modified version of a lottery choice task (Fehr and Goette, 2007; Gächter et al., 2010). Participants were presented with 12 sets of binary choices and were asked to indicate what they would have preferred: 1) A lottery where they could win or lose different sums of money with a chance of 50% for either. 2) A safe no-bet alternative. Later questions had higher winning sums with no change in the losing amount (i.e., a larger expected value). Loss aversion was measured by participants' switching point (ranging from 1 to 12): the higher this switching point was, the higher the participant's loss aversion tendency. Participants who did not switch to the lottery were given the score of 13.

Recognition and contingency awareness: Participants were presented with individual fractals one by one and were asked three consecutive questions: 1) Did this picture participate in the experiment? 2) Was it used as a background of a house in which you have earned money? 3) Was it used as a background of a house in which you have lost money? Participants were asked to indicate their answer and their certainty by choosing a number between 1 to 5, where 1 is

certain yes, 5 is certain no and 3 stands for not sure. The nine CS-s and CS+s together with nine new fractals were presented in a randomized order and the task was self-paced. This task was designed to assess differences between groups in explicit memory indices following our procedure. The first question was used as a standard recognition measurement and the second and third were used as indicators of contingency awareness.

Entering chosen houses: Participants performed a short task in which they entered three houses, drawn from their choices in the three Binary choice probes, in a similar manner to the Conditioning/Counterconditioning. The houses were randomly drawn from the CS- vs. CS- comparisons. Therefore, participants entered three CS-s (which resulted in no monetary outcome). This task was implemented to resolve the Binary choice probe instructions.

Experimental Design and Statistical Analysis

In this experiment we studied if we can suppress the reinstatement of an appetitive memory using memory retrieval prior to aversive counterconditioning. All participants underwent appetitive conditioning on the first day of the experiment. Then, on the second day of the experiment, only half of the participants underwent a memory retrieval phase, prior to aversive counterconditioning performed by all participants. On the third day, we tested if the reinstatement of the initial appetitive memory was different between the "Retrieval" and control, "No Retrieval" group. Our CSs were computerized houses with a background of different fractal art images. The key dependent variable was assessed using binary choices between the paired/unpaired CSs. We also measured the liking towards the CSs, using fractals liking ratings.

Binary choices between CSs that were obtained for each participant at the end of the first and the second days were used to determine whether to further analyze their results. Since reinstatement could be seen only after successful conditioning and counterconditioning, as manifested by preference of the paired CSs in Day 1, and its abolition in Day 2, we only

included data of participants who exhibited learning of these contingencies. We set the learning criteria as follows: **1)** Successful conditioning manifested as paired choice proportion of 0.55 or higher; **2)** Successful counterconditioning manifested as a lower choice proportion compared to conditioning. Participants who failed to meet these conditions were excluded from further analyses (see Results).

We performed a logistic mixed-effects analysis between groups (Retrieval, No-Retrieval) and stage (conditioning, counterconditioning, reinstatement) with preference toward the CS+s stimuli as the dependent variable. As fixed effects, we entered group and stage (with interaction term) into the model. As a random effect, we had intercepts for participants and for the effect of binary choice outcome. Specifically, we were interested in the interaction between the groups and the last two stages (counterconditioning and reinstatement). The binary choice outcome on each trial was marked as 1 or 0, according to participant's choice of the house paired with monetary gain/loss or not. Choice trials, in which participants failed to respond within the given two seconds, were excluded from the analysis (35 observations, 0.65% of the data). On average 107.3 (SD = 1.28) observations were obtained for each participant.

As the learning criteria were derived from the binary choice outcomes, they could not have guaranteed the particular changes in the liking ratings index following conditioning and counterconditioning, which are mandatory for testing our hypothesis. Additionally, the stimuli in the liking ratings were not identical to the stimuli in the rest of the experiment. Therefore, we decided not to analyze these data.

Recognition scores were calculated as the proportion of correctly recognizing whether a stimulus participated in the experiment or not. Contingency awareness for the winning houses was indexed as the proportion of correctly recognizing whether a stimulus that was included in the experiment was paired with monetary gain. For both indices we collapsed responses of 'I am sure it was' and 'I think it was' and all others were considered as rejections. These memory

indices as well as the loss aversion index were compared between the groups using an independent samples t-test. Contingency awareness for the losing houses was not collected for all participants due to a technical problem and thus was not analyzed. Additional two participants did not perform any part of the Recognition and contingency awareness task.

We pre-determined our sample size (and pre-registered it) to be consistent with those used in previous similar studies. All regression analyses were carried out using lme4 package in R programming language. P-values for the linear regression analysis were estimated using Satterthwaite approximation implemented in the lmerTest package.

Pre-registration: The procedure, hypothesis, sample size, dependent variables and analysis methods of this study were pre-registered (https://osf.io/uqnqz/). To analyze the binary choice outcomes, instead of using a mixed-model ANOVA as originally planned, we performed a logistic mixed-effects analysis as described above since it is the correct analysis for this data.

Data and code sharing: All data and analyses codes are available on osf: https://osf.io/uqnqz/

Results

Fifty participants (25 in each group) out of 84 (41 in the Retrieval group and 43 in the No-Retrieval group) met all learning criteria and were included in the analyses. Nineteen participants did not demonstrate sufficient conditioning while 15 participants demonstrated sufficient conditioning but not counterconditioning. The overall average paired houses (CS+s) choice proportion for participants that were included in the analysis was 0.89 following conditioning and 0.37 following counterconditioning (0.34 in the Retrieval group and 0.41 in the No-Retrieval group).

Binary choice probe (preference)

We used a mixed-effects logistic regression analysis to study the interaction between the learning stages (Stage factor) and the memory retrieval manipulation conducted prior to the counterconditioning stage (Group factor), measured by participants' CSs choices (Table 1).

Analysis of preference for the CSs showed a significant Group × Stage interaction ($\chi^2(2) = 14.28$, p = 0.0008). Following conditioning (Day 1), participants in both groups preferred the CS+s (Figure 3), with no difference between the groups as expected, since there was no different group treatment in this phase (p=0.2542). Following counterconditioning (Day 2) participants tended to avoid the CS+s (Figure 3), as reflected by Stage effects for conditioning and counterconditioning among both groups (Retrieval: OR = 25.59, 95% CI [19.32, 34.26], p < 2E−16; No-Retrieval: OR = 27.43, 95% CI [20.30, 37.54], p < 2E−16). Furthermore, we found no Group effect for the counterconditioning stage (p=0.3036), or a specific interaction between Group and the first two stages (conditioning and counterconditioning) (p=0.7456) as expected, since the retrieval manipulation was not hypothesized to affect counterconditioning.

Re-exposure to the appetitive UCS (Day 3) reinstated the original preference in both groups, resulting in a tendency to prefer the CS+s houses again (Figure 3). This was reflected in a Stage effect between counterconditioning and reinstatement showing greater preference towards the CS+s houses in both groups (Retrieval: OR = 3.93, 95% CI [3.15, 4.93], p < 2E−16; No-Retrieval: OR = 7.09, 95% CI [5.58, 9.06], p < 2E−16).

The most interesting effect was that in the Retrieval group, preference towards the reinforced houses was significantly less reinstated (Figure 3), as supported by a Stage x Group interaction effect between counterconditioning and reinstatement (OR = 0.55, 95% CI [0.40, 0.77], p = 0.0005) and in a Group effect for the reinstatement stage (OR = 0.36, 95% CI [0.15, 0.83], p = 0.0163). These results suggest that the retrieval of appetitive memories before their counterconditioning reduces their capacity to influence preferences.

Loss aversion

Two participants (one in each group) were excluded from this analysis due to choice-inconsistency, namely multiple switching points. No difference was found in loss aversion between the groups ($t(46) = -0.93$, $p = 0.3564$) with an average score of ~5.

Recognition and winning houses contingency awareness

In the recognition task participants in both groups correctly recognized ~97% of stimuli with no difference between groups ($t(46) = -1.40$, $p = 0.1685$). Contingency awareness for winning houses in both groups was not as high (~76%) with no difference between groups ($t(46) = -0.09$, $p = 0.9299$).

Discussion

We developed a novel multi-stage procedure to update appetitive memories in humans using aversive counterconditioning following memory retrieval. We show that induction of aversive counterconditioning shortly after retrieving an appetitive memory, reduces the reinstatement of appetitive preferences in humans. Importantly, the recovery of an appetitive cue-monetary gain memory was diminished only when counterconditioning was given after memory retrieval. The evidence shown here for the ability to update human appetitive memory was obtained using a controlled laboratory procedure, targeting memory dynamics, all induced under laboratory settings in healthy participants. This extends previous attempts demonstrated on pre-existing alcohol memories of human hazardous drinkers (Das et al., 2015b). Furthermore, the current paradigm provides a successful translation of the retrieval-counterconditioning behavioral procedure, previously studied in animal models (Goltseker et al., 2017, 2018).

A plausible explanation for the reduced reinstatement we observed is that the memory retrieval manipulation led to destabilization of the appetitive cue-monetary gain memory. This memory destabilization allowed the aversive cue-monetary loss association to incorporate into the appetitive memory trace, during memory reconsolidation. Thus, the memory was altered, consequently reducing reinstatement. Goltseker et al., (2017) recently established a similar procedure in mice, in which a cue-cocaine memory was first formed in a conditioned place preference (CPP) paradigm, and then counterconditioned with lithium chloride-conditioned place aversion (CPA) following memory retrieval. Similar to our present results, the retrieval-counterconditioning in mice prevented the reinstatement of appetitive cocaine-CPP by a cocaine prime (Goltseker et al., 2017). Critically, in the mouse study, when counterconditioning was given before, 5 hours after, or without memory retrieval, it failed to prevent reinstatement (Goltseker et al., 2017). Moreover, this effect was long-lasting (Goltseker et al., 2017). Together, our findings here alongside the mice study by Goltseker et al., (2017) suggest that the retrieval-counterconditioning procedure involves memory reconsolidation mechanisms.

Aversive counterconditioning has been suggested to be more potent than extinction in suppressing appetitive memories (Van Gucht et al., 2010; Tunstall et al., 2012), and yet its effect may be temporary (Bouton and Peck, 1992; Brooks et al., 1995; Tunstall et al., 2012). Here, we show that when induced after a brief memory retrieval, aversive counterconditioning can suppress the reinstatement of appetitive memories, which is typically seen after counterconditioning. Interestingly, based on the memory recognition data we collected, this procedure neither affected the ability to explicitly recognize the stimuli that played a role in the task, nor the awareness to which stimuli yielded monetary gain during conditioning. We also show that the effect was not due to differences in loss aversion between the groups, which could have potentially explained the differences in reinstatement rates.

In addition to memory updating, the paradigm we constructed provides a valuable demonstration of the processes of counterconditioning and reinstatement. Previous human studies on aversive counterconditioning with laboratory-formed memories, typically employed counterconditioning immediately following conditioning (Baeyens et al., 1989; Van Gucht et al., 2010, 2013; Kerkhof et al., 2011), thus targeting short-term, pre-consolidated memories. Under such conditions, it is possible that aversive counterconditioning interfered with the consolidation of the appetitive memory. In contrast, in the present study, a one-day interval between conditioning and counterconditioning assured that the appetitive memory was already consolidated at the time of counterconditioning.

Reinstatement of the appetitive memories was reduced in the Retrieval group, but not completely abolished. These findings are in line with previous reports, showing that disruption of memory reconsolidation, most frequently leads to suppression of the original behavior, rather than to its complete abolition (Saladin et al., 2013; Lonergan et al., 2016; Germeroth et al., 2017; Xue et al., 2017). It is possible that stronger aversive counterconditioning, and/or more efficient memory retrieval (e.g., by expectancy violation), could have led to a stronger suppression, or even complete abolition, of the reinstatement effect. For example, a previous human study used two consecutive days of retrieval-extinction training to decrease craving of abstinent heroin users (Xue et al., 2012). Das et al. demonstrated that maximizing expectancy violation (prediction error) during memory retrieval before counterconditioning led to a substantial reduction in measures of pre-existing alcohol memories of human hazardous drinkers (Das et al., 2015b, 2018).

Previous studies demonstrated that memory disruption or updating can attenuate relapse and alleviate symptoms of related disorders (Brunet et al., 2008; Xue et al., 2012; Isserles et al., 2013; Saladin et al., 2013; Dinur-Klein et al., 2014; Das et al., 2015b; Soeter and Kindt, 2015; Xue et al., 2017). However, others failed to find such effects with

pharmacological (e.g.,: in fear conditioning - Bos et al. 2014; Spring et al. 2015, in drug addiction - Das et al., 2015a; Pachas et al., 2015) or behavioral manipulations (e.g.,: Soeter and Kindt, 2011; Golkar et al., 2012; Hon et al., 2016; Kredlow et al., 2018). The age and strength of the memory, as well as the manipulation used to reactivate it (Dunbar and Taylor, 2017; Xue et al., 2017), were all pointed out as potential boundary conditions. This may complicate the translation of reconsolidation-disruption manipulations to human studies in clinical populations (Spanagel and Bohus, 2015), and therefore our basic-science procedure allows smoother transitional process.

Maladaptive processing of associative memories has been implicated in several neuropsychiatric disorders, including addiction (Hyman et al., 2006; Milton, 2013), OCD (Gillan et al., 2011), PTSD (Milad et al., 2009; Parsons and Ressler, 2013; Careaga et al., 2016) and phobias (Parsons and Ressler, 2013). Specifically, the reinstatement capacity of associative memories is widely responsible for the persistence and relapsing nature of these pathologies, and for the transient effects of contemporary psychotherapy. For example, relapse in addiction is strongly related to the reinstatement of drug-associated memories (Shaham et al., 2003). Thus, a laboratory procedure to study the reinstatement phenomenon has promising clinical implications. While previous studies mainly focused on reinstatement of aversive memories (mainly fear conditioning) (Schwabe et al., 2014; Lee et al., 2017), we provide here a unique basic-science procedure that successfully induces the reinstatement of appetitive memories.

Finally, the procedure we established here is characterized by a modular structure where it is possible to selectively control and manipulate each of the stages and their different components. Exploiting this property may enable the utilization of our procedure to study similar dynamics of aversive memories or other key mechanisms in the dynamics of associative memories, compare different interventions, reinforcers and measurements, and study the underlying brain mechanisms.

In conclusion, in the past decade, several studies aimed to behaviorally interfere with the reconsolidation of associative memories. Understanding the dynamics of associative memories and their updating mechanisms holds promising clinical implications. Although there is evidence for memory alteration, the updating process is seemingly complicated, and has yet to be fully characterized. Our study, conducted under laboratory-controlled settings, successfully demonstrates appetitive memory updating in humans when employing a novel retrieval-counterconditioning behavioral procedure. Furthermore, it can be used for a wider inquiry of associative memory dynamics, relevant boundary condition and the neural mechanisms involved in the process.

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Figure legends

Figure 1. Experimental procedure outline and design. A. Participants attended 3 experimental stages on 3 consecutive days. **B.** Participants performed a baseline fractal liking ratings procedure. The same procedure also followed the conditioning, counterconditioning and reinstatement stages. **C.** Appetitive conditioning to simulated houses (CSs) was applied through a computerized simulated tour. In each block, participants visited each of the 9 houses in the "neighborhood" once in a randomized order. The houses were divided into 3 equal-sized sets, distinguished by color. One set (the green houses in this illustration) was paired with monetary gain. This task was also used for the aversive counterconditioning on Day 2, in which the conditioned stimuli were paired with monetary loss. A short version of this procedure was also used for both the memory retrieval, where participants visited the paired houses and neither gained nor lost money; during reinstatement, participants visited houses with no background (stimuli), during which they received a monetary gain. **D.** In the probe parts participants had to choose which houses they preferred to enter.

Figure 2. Scheme of conditioning and counterconditioning stimuli assignment. The scheme is demonstrated through one participant's ranking scores. Stimuli were ranked and sorted according to individual ratings in the Baseline fractals liking ratings. Three stimuli of each color (red, green and blue) that are the closest to the overall ranking score mean were used together as the 9 CSs. Then, the average score for each CSs color was calculated within its group. The 6 stimuli that belonged to the colors with the higher and lower averages were used as CS-s and the 3 stimuli of the color with the intermediate average served as the CS+s. CS+ = paired stimulus, CS- = unpaired stimulus, CSs refers to both CS+s and CS-s.

Figure 3. Retrieval prior to counterconditioning reduces the reinstatement of binary choice. Mean proportion of trials during which participants chose paired houses (CS+) over unpaired houses (CS-) following conditioning, counterconditioning and reinstatement. Chance level was 0.5, error bars represent standard error of the mean (SEM). *p<0.05; n=25 per group.

Tables

Table 1. Logistic regression analysis of CS+s choices as explained by Stage, Group and their interaction.

	B	SE	OR	95% CI OR	p
Intercept	-0.36	0.30	0.70	[0.39, 1.25]	0.2275
Conditioning (day 1)	3.31	0.16	27.43	[20.19, 37.27]	0.0000
Reinstatement (day 3)	1.96	0.12	7.09	[5.56, 9.03]	0.0000
Retrieval Group	-0.44	0.43	0.64	[0.28, 1.49]	0.3032
Conditioning X Retrieval Group	-0.07	0.21	0.93	[0.61, 1.42]	0.7455
Reinstatement X Retrieval Group	-0.59	0.17	0.55	[0.4, 0.77]	0.0005

Counterconditioning (day 2) and No-Retrieval group were used as the reference categories for the Stage and Group factors, respectively.

Gera et al., Figure 1

A. General Outline

Day 1 - Conditioning

Liking Ratings: Baseline	Appetitive Conditioning (32 min, 3 house-monetary gain pairings)	Binary Choice Probe 1	Liking Ratings Test 1

Day 2 - Counterconditioning

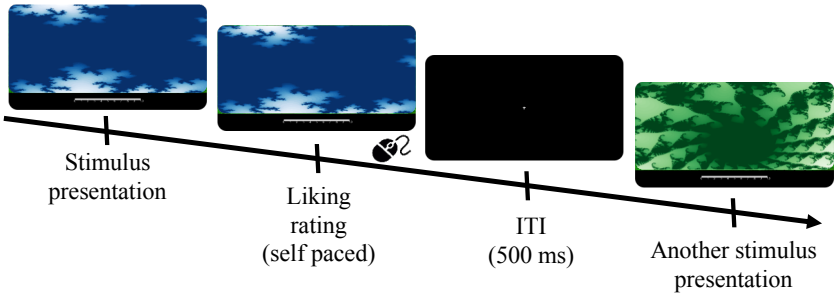
Group 1: Memory Retrieval **Group 2**: No Retrieval	12-min filler task	Counter- conditioning (32 min, 3 house-monetary loss pairings)	Binary Choice Probe 2	Liking Ratings Test 2

Day 3 - Reinstatement

Reinstatement (small monetary gain with no house context)	Binary Choice Probe 3	Liking Ratings Test 3	Post experiment tasks: Loss aversion assessment, Decelerative memory assessment

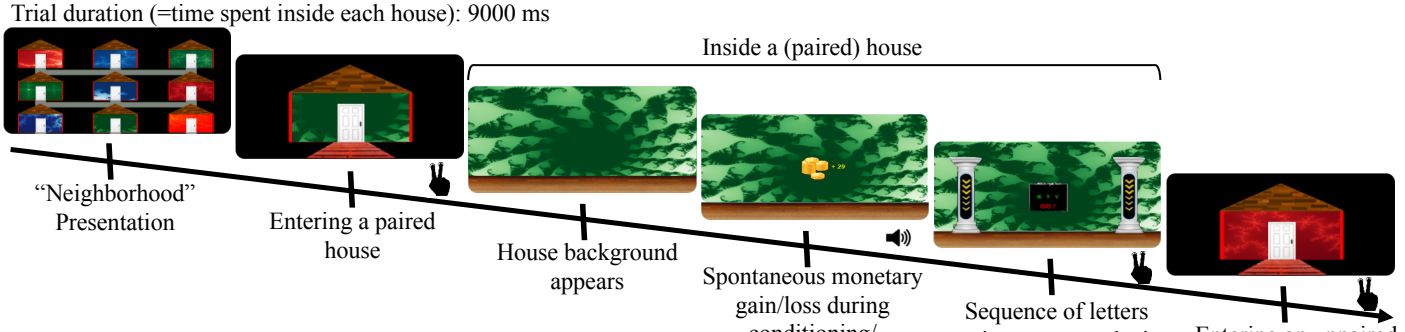
B. Liking Ratings

Trial duration: self-paced



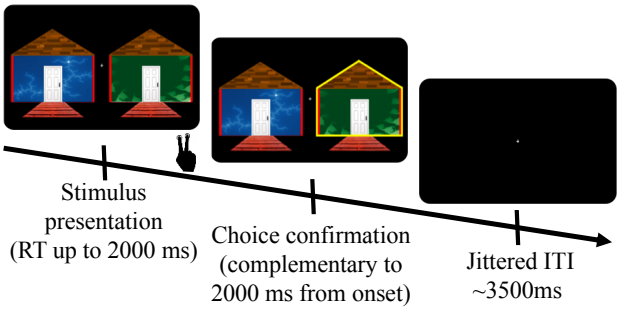
C. Simulated tour: Conditioning/Counterconditioning

Trial duration (=time spent inside each house): 9000 ms

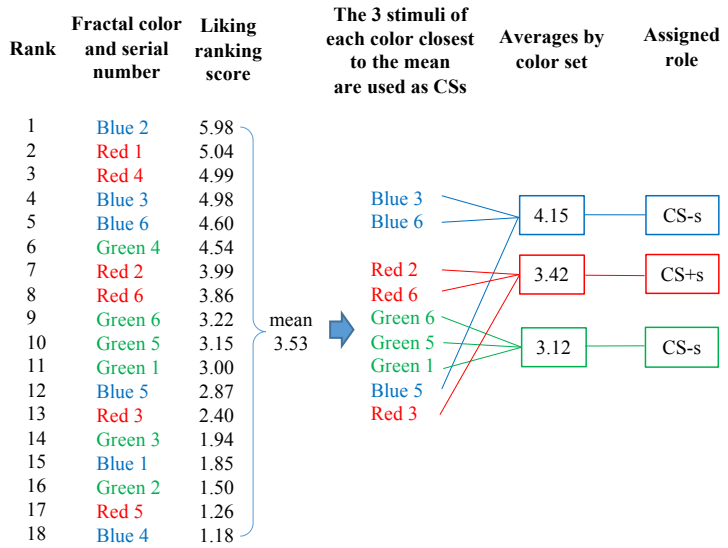
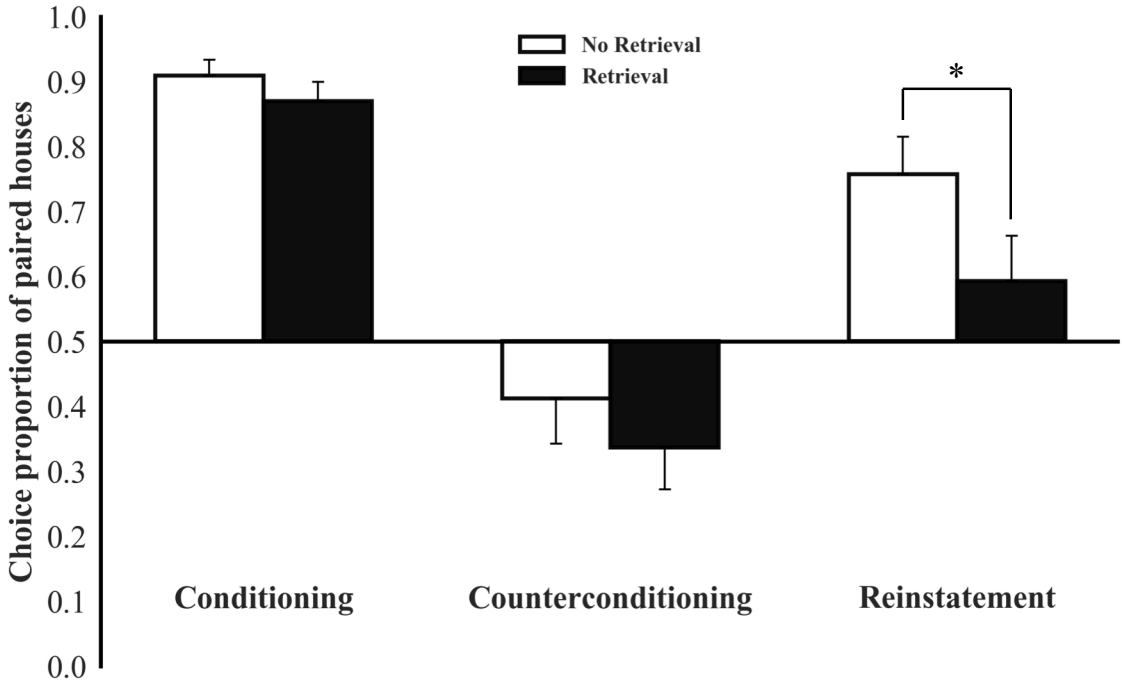


D. Binary choice Probe

Trial duration: 2000 ms



Gera et al., Figure 2



Gera et al., Figure 3