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Positive emotional induction interferes with the reconsolidation of negative autobiographical memories, in women only

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ABSTRACT

After reactivation, a previously consolidated memory can enter into a labile state followed by a re-stabilization process defined as reconsolidation. The aim of this study was to explore whether an existing negative autobiographical memory can be modified by using a non-invasive interference (audiovisual positive preparation) after reactivation and to determine if this effect could be dependent on the reconsolidation process. We found that the presentation of a positive inductor after a negative autobiographical memory reactivation may lead to a change in the emotional information of the original trace and that such effect can be mediated by the reconsolidation process. The modification of the memory has been shown in women only. These results suggest that a positive audiovisual induction may play a potential role in psychotherapeutic techniques for the modification of dysfunctional autobiographical memories.

1. Introduction

Long-term memories are fixed and resistant to disruption after being consolidate (Nader & Hardt, 2009). The reactivation of a stable consolidated memory can render it into a labile (or unstable) state, during which the trace can be strengthened, weakened or modified, under certain conditions. In order to persist, the destabilized trace must undergo a protein synthesis-dependent process referred to as reconsolidation (Finnie & Nader, 2012; Nader, 2013; Nader, Schafe, & LeDoux, 2000; Sara, 2000).

The "reconsolidation window" refers to the time-limited period during which reactivation-induced destabilized memories become susceptible to interference. In fact, interfering manipulations are effective only in a period after reactivation. Once the reconsolidation window is closed, the memory becomes stable again, protecting the stored information from further influence (at least until a proper reactivation cue triggers a new destabilization-reconsolidation round). A lack of effect on the target memory when the interference procedure is applied several hours after reactivation (i.e., outside the reconsolidation window), is considered one of the critical limits for determining that the observed effect is mediated by the reconsolidation process (Nader & Hardt, 2009).

Reconsolidation has been demonstrated to occur in a wide range of species, including humans (Nader, 2015). In fact, this mnemonic process has been reported in human procedural (Walker, Brakefield, Hobson, & Stickgold, 2003), Pavlovian (Kindt, Soeter, & Vervliet, 2009; Schiller et al., 2010) and declarative memories (Forcato et al., 2007; Hupbach, Gomez, Hardt, & Nadel, 2007). Autobiographical memories (a declarative form of memory that encodes, stores and allows the retrieval of mental representations regarding personal experiences with specific time-space coordinates) are considered critical to frame and shape our emotional life, defining who we are and generating an updated sense of the self (Prebble, Addis, & Tippett, 2013); thus, constituting the milestones of social communication. Maladaptive autobiographical memories contribute to psychiatric disorders that actually constitute a significant socio-economic burden (Lane, Ryan, Nadel, & Greenberg, 2014). Current treatments can inhibit but do not get rid of the memory itself, which explains why many patients experience some symptoms again even after initially successful treatment. One potentially promising approach is to alter the original memory by targeting memory reconsolidation, as opposed to inhibiting it. The possibility to destabilize a memory trace opens an opportunity to reduce

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therapeutically the emotional impact of maladaptive memories (Beckers & Kindt, 2017).

In the field of emotions, researchers have suggested that emotion is organized in a biphasic appetitive and defensive motivational system that may act in an additive or a reciprocally exclusive manner (Bradley, Codispoti, Cuthbert, & Lang, 2001). In the same direction within the clinical field, Lane et al. (2014) postulated an integral scheme to apply in clinical settings. They argue that when autobiographical memories are reactivated (and destabilized) they have an emotional component (with its specific valence) that is also reactivated and this is the exact moment at which this memory may incorporate different or new emotional information through the process of reconsolidation. At present, these postulates are being tested in the framework of memory reconsolidation. Some authors have indicated that negative experiences interfere with appetitive memories (Olshavsky et al., 2013; Wang, Zhao, Ghitza, Li, & Lu, 2008; Zhao, Zhang, Shi, Epstein, & Lu, 2009) and also that appetitive experiences dampen reactivated aversive memories (Ferrer et al., 2016; Haubrich et al., 2015). Moreover, a recent report using optogenetic techniques to reactivate emotionally contrasting memories, showed a bi-directional switch between both types of mnemonic traces (Redondo et al., 2014).

Only a few studies within the reconsolidation framework have shown that autobiographical memories can be modified after retrieval (Kredlow & Otto, 2015; Schwabe & Wolf, 2009, 2010). However, none of those works on autobiographical memories have experimentally assessed the effect of interference procedures considering the time-limited period of memory vulnerability after reactivation (i.e., the reconsolidation window). Considering this scenario, in the present study we controlled whether the post-reactivation effect is time-dependent since we hypothesized that a negative autobiographical memory can be modified through the process of reconsolidation by an emotionally positive experience only when the positive experience occurred inside the reconsolidation window.

2. Materials and methods

2.1. Participants

One hundred and ninety-five volunteer students, aged 18–35 (M = 21.21, SD = 3.06), participated in this study. The participants were asked to refrain from eating, doing an intense physical activity and drinking alcohol within two hours before each experimental session. All subjects were randomly assigned to the different groups and tested individually. We asked the participants if they were diagnosed with some serious illness and were asked to report if they were receiving psychological or psychiatric treatment. Participants with serious illnesses, serious psychological disorders and those who consumed pills in a chronic way were excluded from the sample. Women were asked about their menstrual cycle. The study was conducted according to human research guidelines and was approved by the Ethics Committee of the National Clinical Hospital from Córdoba, Argentina. All participants provided a written informed consent prior to the experiments and did not receive any monetary compensation for their participation in the study.

2.2. Procedure

Four experiments were run. The first two experiments were performed to establish the essential parametrical conditions of our study in order to have a method for analyzing the emotional and non-emotional content of the autobiographical memories (Experiment 1) and determining the effectiveness of our emotional and non-emotional inductors (Experiment 2). Experiment 3 was run to determine if a positive audio-visual presentation can modify a negative (angry) autobiographical memory and Experiment 4 was carried out to establish if the detrimental effect on the autobiographical memories depends on reconsolidation process.

2.2.1. Experiment 1

This experiment lasted 1 day. In this experiment, participants' memories were retrieved with one of the four adjectives ("angry", "sad", "happy" or "busy"). N = 10 men and 10 women for each group.

2.2.2. Experiment 2

This experiment lasted 1 day. In this experiment participants were exposed first to the neutral inductor and after that a SAM scale was completed. Two minutes later they were exposed to the positive inductor and were instructed to complete again the SAM scale. N = 11men and 10 women.

2.2.3. Experiment 3

This experiment has 3 experimental days. On day 1 the participants' memories were retrieved with the "angry" adjective and 10 min later they received an induction (positive or neutral). On day 2, 7 days after day 1, the subjects were tested. On day 3, 30 days after day 1, they were re-tested. Group were as follows: men positive inductor (M/PI) (N = 12), men neutral inductor (M/NI) (N = 10), women positive inductor (W/PI) (N = 12) and women neutral inductor (W/NI) (N = 11).

2.2.4. Experiment 4

This experiment has 3 experimental days. On day 1, 4 different groups were formed as function of the presentation of the inductor: the first group R/NI (N = 12) the inductor was not presented after reactivation, in the second group NR/I (N = 13), the inductor was presented but the memory was not retrieved, in the third group R/10 MIN (N = 11), the interference was presented 10 min after memory reactivation and in R/6H group (N = 13) the positive interference was presented 6 h after reactivation. Seven days later, the four groups were tested.

2.3. Reactivation (day 1)

In order to reactivate the autobiographical memories, we used a modified version of the autobiographical memory cueing test (AMT) (Williams & Broadbent, 1986). After completing the informed consent, participants were shown a written adjective ("angry", "sad", "happy" or "busy", depending on the experiment and experimental group). They were instructed to remember, in as much detail as possible, a specific episode related to the presented adjective, including a specific time and place from their own past, in which they had actively participated. Subjects were asked to remember events that were at least 7 days and from 5 years ago at most, and they had 4 min to write down the event. After that, (regardless of having or not finished writing), they were asked to give a title to the memory to facilitate its retrieval in the next experimental days. Additionally, we asked the participants about the age of the memory.

2.4. Test (day 2)

Seven days after memory retrieval the subjects returned to the experimental room and they were shown the title of their remembered event and were instructed to write again what they remembered about it.

2.5. Re-test (day 3)

Thirty days after day 1 (retrieval session) participants were subjected to the same treatment as on experimental day 2.

2.6. Emotional induction

With the objective of inducing a positive or a neutral (control) mood

state, we created two audiovisual clips. We selected 80 images from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008), taking into account the Spanish validation (Vila et al., 2001), and two classical music fragments (Mitterschiffthaler et al., 2007) to make the clips. The positive induction consisted of 40 positive IAPS images (1340, 1721, 1731, 2055.2, 2057, 2058, 2071, 2165, 2208, 2209, 2216, 2222, 2224, 2311, 2331, 2341, 2346, 2352, 2387, 2395, 2655, 4622, 4623, 4626, 4656, 4669, 4670, 4672, 4676, 4687, 5779, 5811, 5831, 7220, 7289, 7325, 8185, 8461, 8496, 8497 (we selected images that presented values above 7 point in average in the valence SAM scale (Vila et al., 2001)) presented for 10 s each and a fragment of the "Blue Danube" as background. The neutral induction consisted of 40 neutral IAPS images (2214, 2215, 2372, 2393, 2394, 2499, 2514, 2516, 2579, 2745, 2749, 2780, 2850, 2880, 2890, 5130, 5395, 5994, 7004, 7020, 7031, 7037, 7038, 7041, 7095, 7096, 7160, 7161, 7175, 7180, 7182, 7183, 7185, 7187, 7237, 7491, 7503, 7504, 7950, 9700 (we selected images that presented values between 4 and 5 points in average in the valence SAM scale (Vila et al., 2001)) presented for 10 s each and a fragment of "Moonlight" as background.

2.7. Autobiographical memory evaluation

The method used in this work to rate the memories was an adaptation of the procedure used by Hassabis, Kumaran, Vann, and Maguaire (2007) to analyze the content of an autobiographical memory. One point was given for each remembered detail (i.e. for each present entity, localization or time reference, sensorial description or thoughts/emotions/actions (TEAs)). Each detail was given only one point, even if it appeared once or several times. In particular, the TEAs were classified as positive, neutral or negative. This modification to the Hassabis et al. (2007) procedure was tested in experiment 1 in order to verify its utility to discriminate emotionally positive, negative or neutral mnemonic information. Written memories were evaluated by 3 independent raters. The inter-rater reliability was established selecting 40 random cases from experiment 1; sex and kind of event (angry, sad, happy and busy) were balanced. The agreement between the three raters was very high (interrater reliability $r_{icc} = 0.98$). Discrepancies between them were discussed until an agreement was reached.

2.8. Subjective assessment

2.8.1. Self-Assessment Manikin (SAM)

Only in experiment 2, we used the valence and arousal dimensions of the SAM scale (Bradley & Lang, 1994). Subjects were instructed to rate between a continuous range of 9 points. For *valence*, number 1 represents the negative pole and the positive one was represented by number 9. Here the positive pole is represented by a happy face and the negative 1 by an unhappy face. In the case of *arousal*, the range was the same than the valence, where number 1 represented the calm or relaxed face and number 9 represented the excited or activated state. The calm pole was represented by a relaxed, sleepy face and the activated state was represented by an excited wide-eyed face.

2.8.2. Profile of Mood States (POMS)

In experiment 1, 3, and 4, we used the Spanish version of the POMS (Andrade, Arce, & Seaone, 2002). The POMS has 48 items measuring six mood factors or states: *anger, depression, tension, fatigue, vigor, and friendliness*. Each item was rated following a 0 (nothing) to 4 (very much) Likert scale. The participants were told to respond about how they felt the last week including the present day. They completed the questionnaire before entering the experimental room.

2.9. Statistical analysis

Results were expressed as mean ± SEM of different kind of details. Significant ANOVAs (one way, factorial and mixed) were followed by Tukey Test or planned contrast for post-hoc analysis. Furthermore, the unpaired and paired two tailed *t*-test was used. In all cases, $P < 0.05$ was the statistical threshold. The homogeneity (Levene test or Mauchley Sphericity test were used depending on the case) and normality (Kolmogorov Smirnov test) principles were verified in all the variables of the four experiments. When the principles were violated, non-parametrical tests were used, Kruskal-Wallis (Multiple comparisons of mean ranks as Post-hoc) or Mann Withney tests depending on the case. In all cases, $P < 0.05$ was the statistical threshold.

3. Results

3.1. Experiment 1

3.1.1. Validation of a new method to analyze the emotional and non-emotional content of autobiographical memories

This experiment was designed to validate a new method in order to asses the emotional content of an autobiographical memory. Previous methods were used to analyze these kinds of memories considering a series of items which are counted as memory contents. These items are generally present entities (objects, animals or persons), time and place references (i.e., day or night; out in the street or inside the kitchen), thoughts/emotions/actions (TEAs), and sensory descriptions (i.e., a blue bag or a cold beverage) (Hassabis et al., 2007; Kredlow & Otto, 2015; Schwabe & Wolf, 2009, 2010; Squire et al., 2010). However, none of those methods have categorized TEAs according to their emotional valence (i.e. neutral, negative or positive). Here, we adapted the method reported by Hassabis et al. (2007) in order to analyze the content of autobiographical memories and classify the TEAs into positive, negative or neutral. One point was given for each detail remembered (i.e. for each present entity, space or time reference, sensorial description or TEAs).

The experiment was run in one day and participants only completed the Autobiographical Memory Test (AMT, see Materials and Methods). One out of four adjectives: *angry, sad, busy* or *happy* was shown and subjects had 4 min to write down a personal episode related to it. They were instructed to remember, in as much detail as possible, one specific event from their own past for the adjective shown, including time and place. Our hypothesis was that if memories differ in their valence they should also differ in the amount of positive, negative or neutral emotional content.

As shown in Fig. 1B, women's memories tended to be more detailed than men's. A factorial ANOVA (adjective by sex) on total details (including present entities, space or time references, sensorial descriptions and TEAs), revealed no effect of adjective [$F(3,72) = 0.83$, $P > 0.05$], an effect of sex [$F(1,72) = 25.56$, $P < 0.01$], and no interaction between sex and adjective [$F(3,72) = 1.10$, $P > 0.05$]. Therefore, further analyses will be performed separating the sexes. Accordingly, this effect was previously reported in the field of autobiographical memory

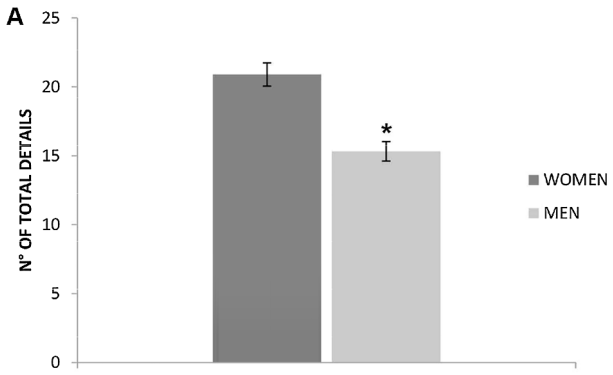

Fig. 1. Regardless of the adjectives, women retrieved more details than men. Mean of total details. (N = 40 per group). ± SEM. *, $p < 0.05$.

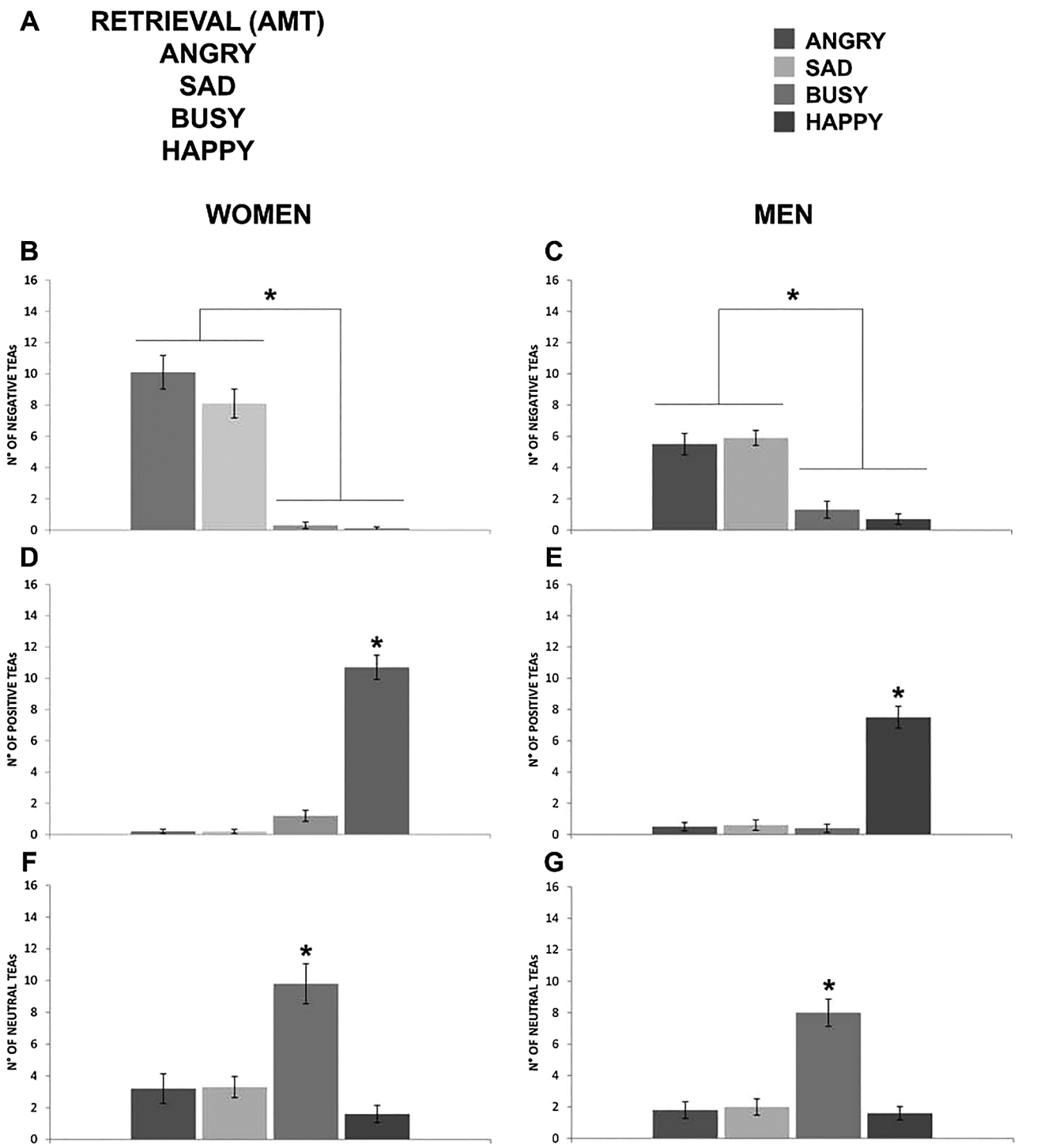

Fig. 2. (A) Experimental protocol. (B–G) Different numbers of details were found as a function of the kind of adjective and the informational content observed. Mean of negative TEAs (B, C), positive TEAs (C, D) and neutral TEAs (E, F). (N = 10 per group). ± SEM. *, $p < 0.05$.

(Bloise & Johnson, 2007; Jaques, Conway, & Cabeza, 2011; Ros & Latorre, 2010).

One-way ANOVAs (adjective as the factor) were run on all category details, separated by sex.

3.1.2. Details analyzed in women's memories

A one-way ANOVA on **negative TEAs** revealed an adjective effect at retrieval [$F(3,36) = 52.18$, $P < 0.01$]. Post-hoc analysis revealed that *sad* and *angry* memories exhibited significantly more negative TEAs than *busy* and *happy* memories. Homogeneity and normality principles were violated. Additionally, a Kruskall-Wallis revealed an adjective effect [$H(3) = 32.24$, $P < 0.01$]. The Post-hoc analysis showed the same pattern as ANOVA Post-hoc (Fig. 2B).

The ANOVA on **positive TEAs** revealed an adjective effect [$F(3,36) = 136.18$, $P < 0.01$]. Post-hoc analysis demonstrated that a *happy* memory exhibited significantly more positive TEAs than *angry*, *sad* and *busy* memories. Homogeneity and normality principles were violated. Additionally, a Kruskall-Wallis revealed an adjective effect [$H(3) = 28.72$, $P < 0.01$]. The Post-hoc analysis showed the same pattern as ANOVA Post-hoc (Fig. 2D).

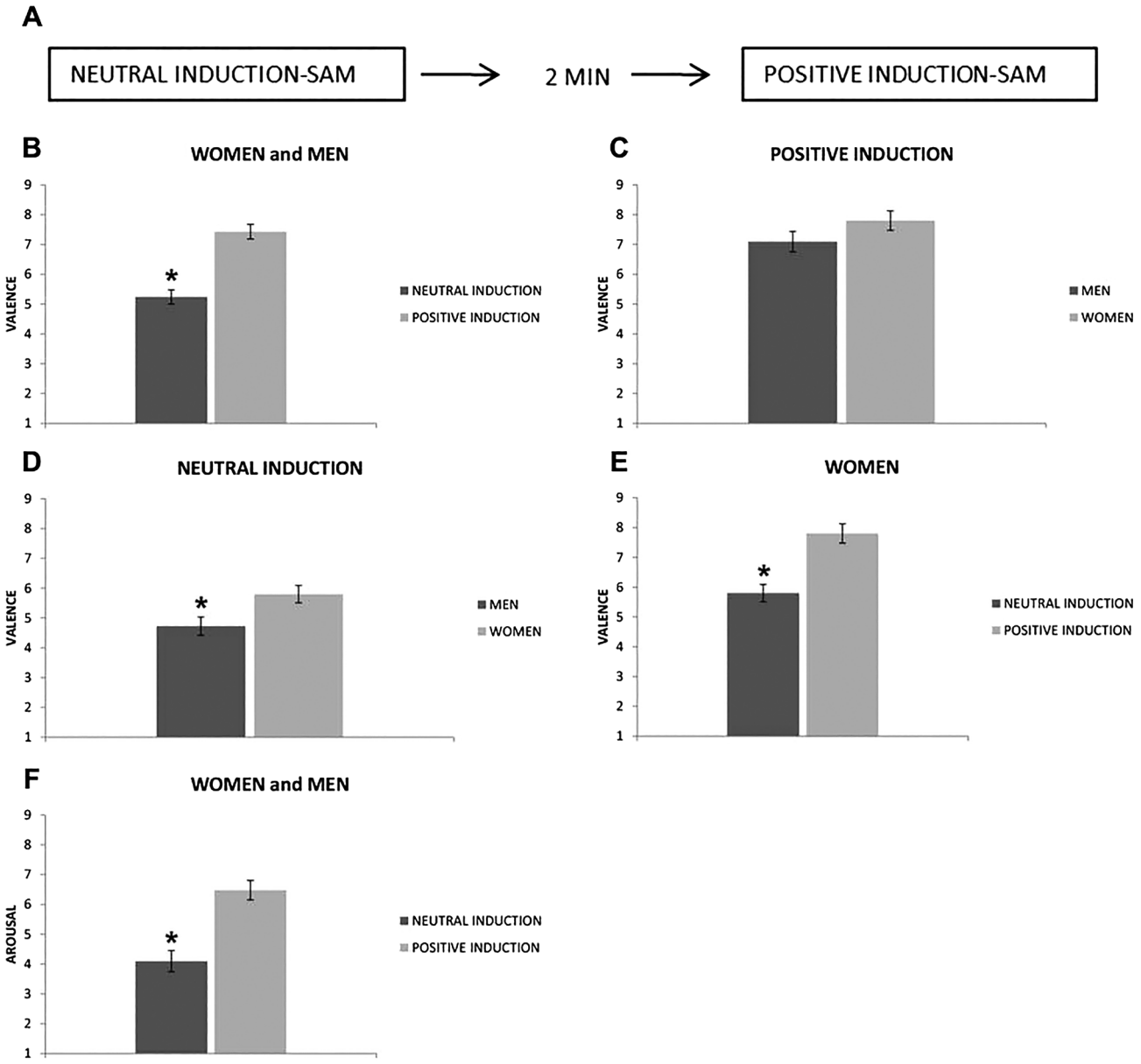

Fig. 3. (A) Experimental protocol. (B) In valence, for women and men, neutral and positive ratings differed, relative to scale ratings. (C) Women and men did not differ when they rated the positive inductor. (D) Men and women differed when they rated the neutral inductor. (E) Finally for valence, it was demonstrated that women rated the inductors differentially. (F) In arousal both sexes rated the inductors differentially. Mean of valence (B-E) and arousal (F). (N = 10 women and 11 men). ± SEM. *, $p < 0.05$.

On **neutral TEAs** a one-way ANOVA demonstrated an adjective effect [$F(3,36) = 16.64$, $P < 0.01$]. *Busy* memories exhibited significantly more neutral TEAs than *angry*, *sad* and *happy* memories. The homogeneity principle was violated. Additionally, a Kruskall-Wallis revealed an adjective effect [$H(3) = 19.75$, $P < 0.01$]. The Post-hoc analysis showed the same pattern as ANOVA Post-hoc (Fig. 2F).

The ANOVAs on the rest of the categories did not show an adjective effect [$F(3, 36) = 2.19$, $P > 0.05$].

3.1.3. Details analyzed in men's memories

A one-way ANOVA on **negative TEAs** demonstrated an adjective effect [$F(3,36) = 26.92$, $P < 0.01$], and the post-hoc analysis showed that *angry* and *sad* memories presented more negative TEAs than the positive and neutral memories. (Fig. 2C).

For **positive TEAs** the one-way ANOVA demonstrated an adjective effect [$F(3,36) = 65.08$, $P < 0.01$], with post-hoc analysis revealing that a *happy* memory had more positive TEAs than *angry*, *sad* and *busy* memories. The normality principle was violated. Additionally, a Kruskall-Wallis revealed an adjective effect [$H(3) = 26.51$, $P < 0.01$]. The Post-hoc analysis showed the same pattern as ANOVA Post-hoc (Fig. 2E).

A one-way ANOVA on **neutral TEAs** revealed an effect adjective [$F(3,36) = 25.89$, $P < 0.01$]. Here, the post-hoc analysis revealed that a *busy* memory had more neutral TEAs than *angry*, *sad* and *happy* memories (Fig. 2G).

The ANOVA on the rest of the categories, all together, did not show an adjective effect [$F(3,36) = 2.75$, $P > 0.05$].

Finally, one-way ANOVA (adjective as the factor) were run on the six factors of the POMS questionnaire data, in order to discard possible influences of previous emotional states on the day of the experiment. There was no significant effect on any one of the six factors, neither on women nor on men ($Fs < 1.34$, $Ps > 0.05$). In men, *depression* and *friendliness* factors were not homogeneous. Additionally, a Kruskal-Wallis on both factors was run. The groups did not differ in *depression*

[H (3) = 0.53, P > 0.05] neither in *friendliness* [H (3) = 1.86, P > 0.05].

Summarizing, this experiment showed that the emotional content of the retrieved memories differed according to the adjective shown (*angry, sad, busy* or *happy*). Furthermore, this was revealed by classifying TEAs according to its emotional valence, demonstrating that this variation on the Hassabis et al. (2007) procedure is appropriate to measure diversity in the retrieved emotional content. Additionally, this data revealed that the total amount of retrieved information (all categories combined) did not differ according to the emotional content of the retrieved memory. In other words, subjects retrieved similar amounts of information, regardless of its emotional content and only according to the experimental demand. However, there was a sex difference in total amount of retrieved information, an effect previously reported in autobiographical memories (Bloise & Johnson, 2007; Jaques et al., 2011; Ros & Latorre, 2010).

3.2. Experiment 2

3.2.1. Evaluation of the emotional and non-emotional inductors

In Experiment 2, with the aim of inducing a positive and a neutral (control) mood state, we created two audiovisual clips. We selected eighty images from the International Affective Picture System (IAPS) (Lang et al., 2008), and two classical music fragments (Mitterschiffthaler et al., 2007) to make the clips (see Section 2). In order to test the emotionality of the inductors, we evaluated the valence and arousal of the inductors using the Self Administrated Maniquim scale (SAM) (see Section 2). Subjects were shown first, the "neutral" preparation and after that, a SAM scale. Two minutes later, they were shown the "positive" preparation and the SAM scale again. We analyzed valence and arousal. As expected, participants rated the positive emotional inductor with significantly higher scores than the neutral emotional inductor suggesting that the mood induction was successful.

A mixed-ANOVA (sex and session as factors) on valence, revealed significant effect on sex [F (1,19) = 9.86, P < 0.05] (women outperformed men in punctuation), session [F (1,19) = 39.03, P < 0.01] (subjects rated the positive inductor higher than the neutral one), and no interaction between sex and session [F (1,19) = 0.27, P > 0.5].

An unpaired two-tailed *t*-test was run to determine if women and men differed in the evaluations of each inductor. This analysis revealed no sex effect on the valence of the positive inductor [t (19) = −1.49, P > 0.05] (Fig. 3C) and a sex effect on the valence of the neutral inductor [t (19) = −2.52, P < 0.05]; women tended to evaluate the neutral inductor significantly more positively than men did. (Fig. 3D). Finally, a paired two tailed *t*-test for dependent variables revealed that women differ in their evaluation of the inductors [t (9) = −4.73, P < 0.01]; neutral is in effect rated as neutral and positive as positive (Fig. 3E).

A mixed-ANOVA (sex and session as factors) on arousal, revealed no sex effect [F (1,19) = 0.76, P > 0.05], a session effect [F (1,19) = 38.71, P < 0.01], and no interaction between both factors [F (1,19) = 0.62, P > 0.05]. The neutral inductor was rated with values around 5 and the positive inductor with higher ratings (Fig. 3F).

To sum up, when participants saw the inductors, they rated the positive inductor with higher scores than the neutral inductor both for valence and arousal, as hypothesized. Furthermore, the neutral inductor was rated with values around 5 in both valence and arousal. Thus, confirming the neutral valence and arousal of the inductor.

3.3. Experiment 3

3.3.1. A negative autobiographical memory can be modified by a positive audiovisual presentation after reactivation

This experiment was designed to evaluate whether an existing negative autobiographical memory can be modified by interference upon retrieval using a positive audiovisual experience. If retrieval triggers destabilization of the original memory, the positive new information presented after the recall session might render the original memory less negative through the restabilization-reconsolidation process. The experiment was performed on 3 non-consecutive days: day 1 (retrieval session), day 2 (test – 7 days after retrieval session), and day 3 (retest – 30 days after retrieval session). On day 1, participants were randomly assigned to two experimental groups: POSITIVE INDUCTOR (PI) and NEUTRAL INDUCTOR (NI). Participants' memories were reactivated by means of the AMT by the presentation of the negative adjective "*angry*" and they were instructed to remember, in as much detail as possible, one specific event from their own past including a specific time and place and to write down the event in 4 min. After that, they were asked to indicate when each event had occurred and to give each memory a title. Ten minutes after reactivation half of the subjects were shown the positive audiovisual inductor (PI group) and the other half was shown an equivalent neutral audiovisual inductor (NI group). Participants' memories were tested 7 and 30 days later by means of the presentation of the title of the event and they had again 4 min to write down the event.

As in experiment 1, women outperformed men in total details on day one. An unpaired *t*-test on total details demonstrated that women recalled more details than men [t (43) = 2.37, P < 0.05]. Therefore, the analyses were run separately for each sex. Groups were separated by sex. Four groups were defined: men/positive inductor (M/PI), men/neutral inductor (M/NI), women/positive inductor (W/PI) and women/neutral inductor (W/NI). Mixed-ANOVAs were run for each memory component.

3.3.2. Details analyzed in women's memories

As shown in Fig. 4B the presentation of the positive inductor after memory reactivation significantly reduced the number of total details 7 and 30 days later but this difference was not revealed when compared positive vs. neutral control groups on days 1, 2 or 3.

A mixed-ANOVA (induction and session as factors) **on total details** revealed no induction effect [F (1,21) = 0.42, P > 0.05], no session effect [F (2,42) = 2.36, P > 0.05], but a significant interaction between both factors [F (2,42) = 5.24, P < 0.01]. To analyze the interaction, planned comparisons were run; they revealed that groups (W/PI and W/NI) did not differ on days 1, 2 and 3 [Fs < 2.24, Ps > 0.05]. For the W/PI group the number of total details decreased significantly from day1 to day 2 [F (1,21) = 10.75, P < 0.01] and from day 1to day 3 [F (1,21) = 7.12, P < 0.05]. For the W/NI group there was no difference from day 1 to day 2 [F (1,21) = 1.78, P > 0.05], neither from day 1 to day 3 [F (1,21) = 0.02, P > 0.05].

On the number of **total TEAs** (Fig. 4 D), the presentation of a positive inductor reduced significantly the number of total TEAs 7 and 30 days later, but there was no difference when compared with the group that received the neutral inductor on the number of **total TEAs** on days 2 or 3 compared to day 1. A mixed-ANOVA was carried out (induction and session as factors) on **total TEAs**. This analysis revealed no effect induction [F (1, 21) = 0.78, P > 0.05], but a session effect [F (2, 42) = 3.31, P < 0.05] and an interaction between both factors was revealed [F (2, 42) = 7.27, P < 0.01]. Planned comparisons were run to analyze the interaction. Groups W/PI, W/NI did not differ on day 1, 2 or 3 [Fs < 3.37, Ps > 0.05]. The presentation of a positive inductor reduced the total TEAs from day 1 to day 2 [F (1,21) = 9.97, P < 0.01], and from day 1 to day 3 [F (1,21) = 16.78, P < 0.01]. For the group that received the neutral inductor there was no change in TEAs from day 1 to day 2 [F (1,21) = 2.56, P > 0.05], neither from day 1 to day 3 [F (1,21) = 0.10, P > 0.05].

Remarkably, when analyzing the **negative TEAs** (Fig. 4F) we found not only a reduction within the group (for the W/PI group) but also a difference between groups (W/PI and W/NI) on days 2 and 3.

A mixed-ANOVA (induction and session as factors) **on negative TEAs** revealed no induction effect [F (1,21) = 4.01, P > 0.05], a session effect [F (2,42) = 8.28, P < 0.01], and an interaction between

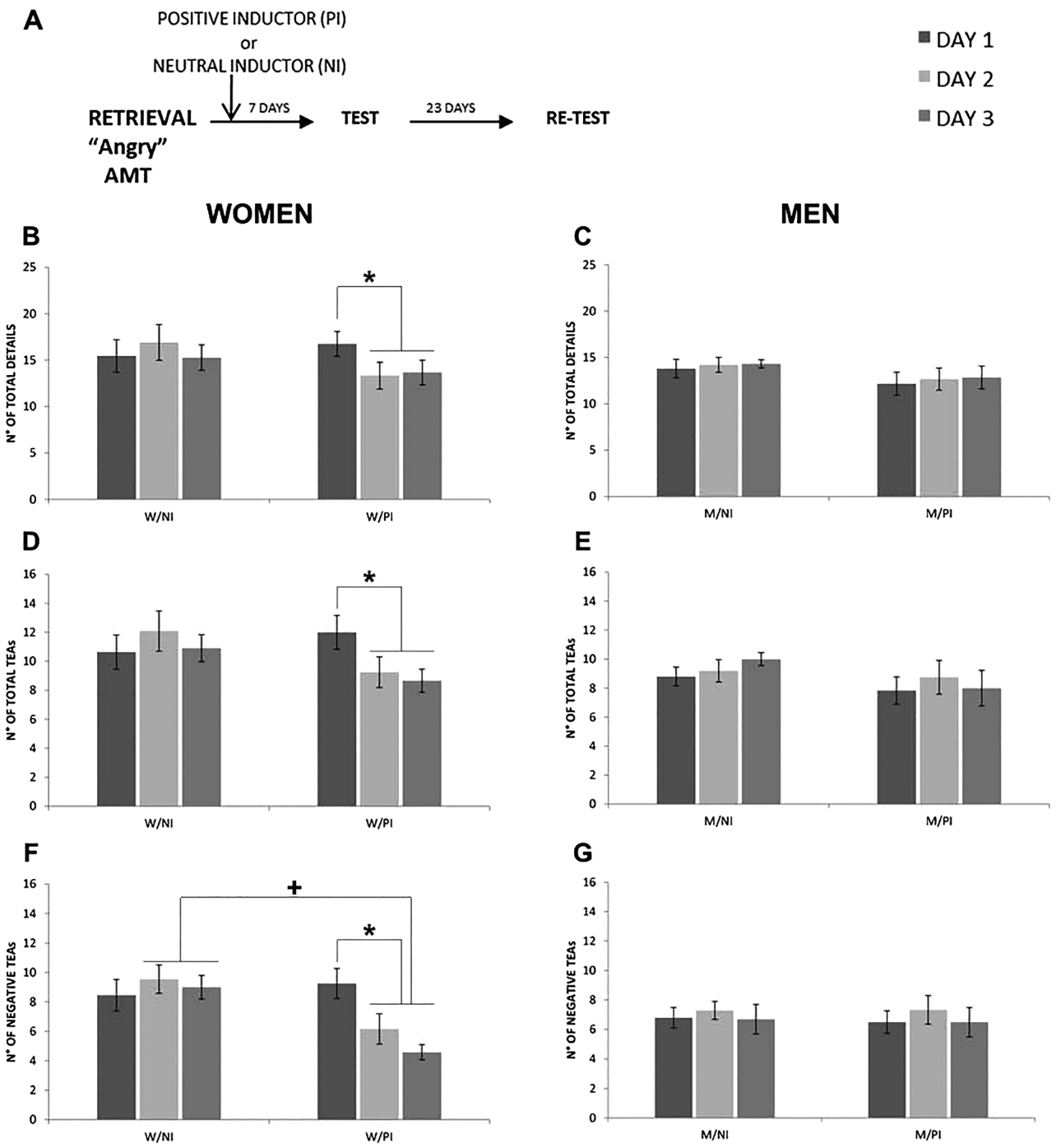

Fig. 4. (A) Experimental protocol. In women, the presentation of the positive induction after reactivation reduced significantly the number of total details (B) and Total TEAs (D) from day one to day two and from day one to three, but on days two and three they were not different to the respective control groups. The number of negative TEAs (F) decreased from day one to day two and three as did the previous details, but it was too different to the respective controls on days two and three. For men, the number of total details, total TEAs and negative TEAs did not change in any condition (C, E and G). Mean of total details (B, C), total TEAs, (D, E) and negative TEAs (F, G). (N = men positive (12), men neutral (10) women positive (12) women neutral (11). ± SEM. *, $p < 0.05$.

both factors [$F(2,42) = 14.84$, $P < 0.01$]. Planned contrasts showed that the groups did not differ on day 1 [$F(1,21) = 0.28$, $P > 0.05$], but differed on days 2 and 3 [$Fs > 5.62$, $Ps < 0,05$]. The presentation of the positive inductor (W/PI) reduced significantly the number of negative TEAs from day 1 to day 2 [$F(1,21) = 20.33$, $P < 0.01$] and from day 1 to day 3 [$F(1,21) = 50.16$, $P < 0.01$]. This effect was not observed on W/NI group.

Mixed-ANOVAs on the **other details** (i.e. positive TEAs, neutral TEAs, entities present, sensorial descriptions, temporal descriptions, spatial relationships) (induction and session as factors) did not reveal an induction effect [$F(1,21) = 0.55$, $P > 0.05$], no session effect [$F(2,42) = 0.24$, $P > 0.05$], or interaction between both factors [$F(2,42) = 2.54$, $P > 0.05$].

3.3.3. Details analyzed in men's memories

In men, for each set of details (i.e. total details, total TEAs, negative TEAs and other details) mixed ANOVAs on each set of detail (Induction and session as factors) were carried out. No induction effect was revealed [$Fs < 2.82$, $Ps > 0.05$], neither was a session effect [$Fs < 1.66$, $Ps > 0.05$] or interaction between both factors

[Fs < 2.05, Ps > 0.05] (Fig. 4C, E and G).

Two-tailed t-tests, independently from the groups, were run to analyze the mood states. The six factors of the POMS questionnaire did not differ between groups on experimental days 1, 2, or 3 for women (Ts < 1.95 Ps > 0.05). Only in the *fatigue* factor, on day 3, the homogeneity was violated. The Man Whitney test indicated that the groups did not differ in the *fatigue* factor on day 3 [U = 40.50, P > 0.05]. The six factors of the POMS questionnaire did not differ between groups on experimental days 1, 2 or 3, for men (Ts < 1.74, Ps > 0.05). Mood states did not appear to explain Experiment 3 results.

Summarizing, the positive inductor dampened a negative memory in women, but this effect was really demonstrated when compared to negative TEAs; the decrease in total details and total TEAs is dependent on negative TEAs. Furthermore, since the rest of details analyzed did not change during sessions, this validates the finding that only the emotional content can be modulated. Finally, in men, the memory was retrieved but apparently not destabilized.

3.4. Experiment 4

3.4.1. The modification of a negative autobiographical memory is dependent on the memory reconsolidation process

The present experiment was designed to evaluate whether the effect of the positive experience post-retrieval on the negative autobiographical memory could **be dependent on the reconsolidation process**; i.e. we explored whether the effect of the emotional inductor was time-dependent and whether the reactivation of the memory was necessary to modify the emotional content of the trace (Duvarci & Nader, 2004; Walker et al., 2003). Therefore, an additional group was carried out in which the inductor was not presented.

Participants were randomly assigned to one of the four experimental groups taking into account the precise moment in which each group received the positive inductor: REACTIVATION NO INDUCTOR(R/NI), NO REACTIVATION INDUCTOR (NR/I), REACTIVATION FOLLOWED 10MIN BY THE INDUCTOR (R/10 MIN) and REACTIVATION FOLLOWED 6HOURS LATER BY THE INDUCTOR (R/6H). On day one, in the first group (R/NI) the inductor was not presented after reactivation; in the second group (NR/I), the inductor was presented but the memory was not retrieved; in the third group (R/10 MIN), the interference was shown 10 min after memory reactivation; and in the R/6H group the positive interference was shown 6 h after reactivation. Seven days later, the four groups were tested.

Since the groups were different at the moment of retrieval and test (there is no retrieval for the second group- NR/I, so there are 3 groups on day one and 4 groups on day 2) we decided to analyze the retrieval and test sessions independently, using a one-way ANOVA in each case, and post-hoc Tukey, for all the components of the memories.

The effect of the positive inductor at different times (R/NI, NR/I, R/10 MIN, R/6H) related to reactivation of the negative autobiographical memory on the number of total details, total TEAs, and negative TEAs is shown in Fig. 5B–D, respectively.

As shown in Fig. 5B, there is no positive inductor effect after retrieval on the number of total details in any group at the time of the retrieval and the test. A one-way ANOVA (inductor as the factor) on **total details** revealed no inductor effect [F (2,33) = 1.49, P > 0.05] at the time of the retrieval and no inductor effect [F (3,45) = 2.14, P > 0.05] at the time of the test.

The positive inductor 10 MIN after reactivation session reduced significantly the number of total TEAs (Fig. 5C) and the number of negative TEAs (Fig. 5D) at the test time compared to the rest of the groups.

A one-way ANOVA (inductor as the factor) on **total TEAs** did not reveal an inductor effect at the retrieval [F (2,33) = 0.10, P > 0.05], but an effect in the test was revealed [F (3,45) = 5.23, P < 0.01]. The Post-hoc revealed that the group R/10 MIN differed significantly from group NR/I and group R/NI. This difference was not significantly from group R/6H (P = 0.07).

A one-way ANOVA (inductor as the factor) on **negative TEAs** revealed no inductor effect at the retrieval [F (2,33) = 0.07, P > 0.05] but revealed an effect at the test time [F (3,45) = 9.18, P < 0.01]. A post-hoc Tukey revealed that group R/10 MIN differed from the other control groups. This finding demonstrated that the positive induction modified the negative emotional content of the memory when the proper conditions are reached. In this case, an inductor is provided on a destabilized memory.

One way-ANOVA on the **other details** (i.e. positive TEAs, neutral TEAs, entities present, sensorial descriptions, temporal descriptions, spatial relationships) (induction as factor) did not reveal an induction effect [F (2,33) = 2.06, P > 0.05] at the retrieval. No inductor effect was reached at the test [F (3,45) = 2.25, P > 0.05].

One-way ANOVAs (inductor as the factor) were run to analyze the mood states. The six mood states factors of the POMS questionnaire did not differ between groups on experimental day 1 (the retrieval) or day 2 (the test) for women (Fs < 0.98, Ps > 0.05). In the fatigue factor the homogeneity principle was violated, on day 1. The Kruskal Wallis test demonstrated that the groups did not differ in fatigue factor [H (2) = 0.67, P > 0.05]. In the tension factor, the homogeneity principle was violated on day 2. The Kruskal Wallis test demonstrated that the groups did not differ in the tension factor [H (3) = 0.51, P > 0.05]. In the depression factor, the normality principle was violated on day 2. The Kruskal Wallis test demonstrated that the groups did not differ in the depression factor [H (3) = 1.07, P > 0.05].

In sum, we demonstrated that the effect showed in experiment 3 could be replicated and only the negative emotional content of a negative autobiographical memory could be modified by a positive inductor. Furthermore, we added key evidence to the view that the effect on a negative autobiographical memory probably depends on the reconsolidation process, since in the typical control groups (NR/I, R/NI and R/6H) the memory were not modified. Finally, the differences were revealed only at the test, not at the retrieval (in the negative emotional content). Thus, the participants' memories were totally comparable.

4. Discussion

Two main findings emerged from the present study: first, we demonstrated that retrieval can destabilize a negative autobiographical memory and render it susceptible to be modified by the experience of unrelated positive audiovisual information; and second, this effect is probably dependent on the reconsolidation process. In fact, this effect was noticeable even after one month.

Four experiments support these conclusions. The first two experiments were performed to establish the essential parametrical conditions of our study, to have a method to analyze the emotional and non-emotional content of the autobiographical memories and to determine the effectiveness of our emotional and non-emotional inductors. The other experiments were necessary to meet the criteria mentioned above, the typical reconsolidation preparation.

Experiment 1 showed that different positive ("*happy*"), negative ("*sad* and *angry*"), and neutral ("*busy*") autobiographical memories expressed different kinds of emotional contents. In consequence, we added an emotional evaluation to the method used by Hassabis et al., 2007. Another important result is that women outperformed men in the number of total details; this is interesting because it is a result widely reported in the autobiographical memory field (Bloise & Johnson, 2007; Jaques et al., 2011; Ros & Latorre, 2010; for a review see Andreano & Cahill, 2009).

In Experiment 2 we validated our emotional inductors (neutral and positive); subjects evaluated both: neutral as neutral and positive as positive.

In Experiment 3 both motivational circuits interacted, the appetitive and the aversive one (i.e. the negative autobiographical memory *angry*

A

	DAY 1		DAY 2
	RETRIEVAL	POSITIVE INDUCTOR	TEST
REACTIVATION/NO INDUCTOR	X	-	X
NO REACTIVATION/ INDUCTOR	-	X	X
REACTIVATION/10MIN INDUCTOR	X	X	X
REACTIVATION/6H INDUCTOR	X	X	X

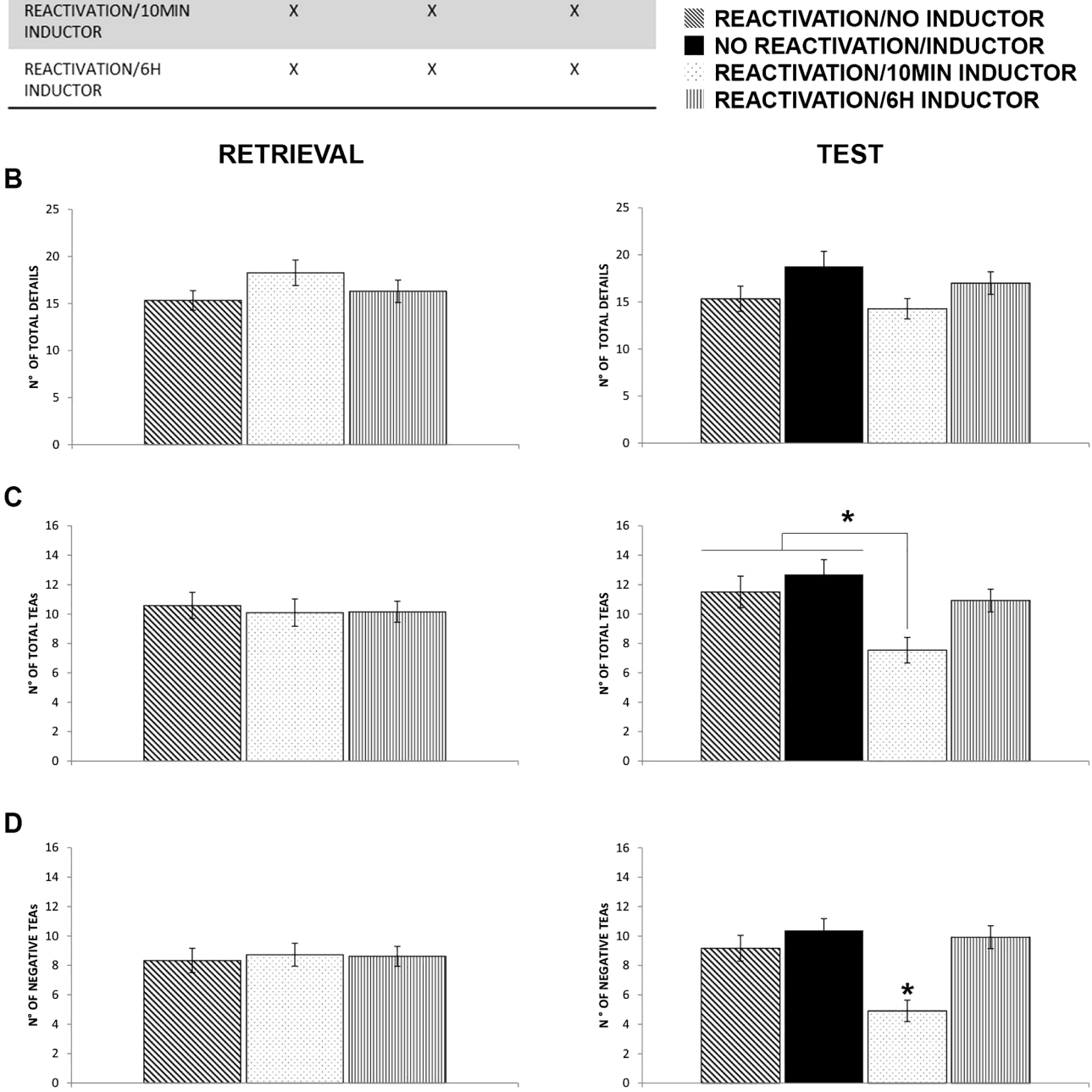

Fig. 5. (A) Experimental protocol. In women, as in Experiment 3 only for negative TEAs, the groups differed from the respective controls (D). Furthermore here we showed that when the positive induction was administered six hours later, the total details (B), total TEAs (C) and negative TEAs (D) did not diminish. Mean of total details (B), total TEAs (C) and negative TEAs (D). (N = R/NI 12, NR/I 13, R/10 MIN 11), R/6H 13). ± SEM. *, $p < 0.05$.

and the positive inductor). The main result of this experiment was that an appetitive experience modifies the emotional content of the negative memory (negative TEAs). The other contents (non-emotional contents) remained unaffected. Similar results were found in fear memory conditioning, where the emotional expression of memory was deteriorated by means of propranolol administered within the reconsolidation window and non-emotional declarative memory information remained unmodified (Kindt et al., 2009; Soeter & Kindt, 2010, 2011). Notably, this interfering influence was maintained for 30 days. Remarkably, this effect was shown only on women. One possible explanation is that men

retrieved their memories but presumably did not destabilize the memory trace; thus, memory became active but unable to incorporate new information under the present conditions. Taking into account our results, we propose that some degree of re-experience in emotional terms is a necessary condition for memory destabilization. In the autobiographical memory field, it is widely reported that women remember more negative facts and amount of details in emotional events than men (Davis, 1999; Fujita et al., 1991; Pohl, Bender and Lachmann, 2005; Ros and Latorre, 2010; Seidlitz and Diener, 1998). Moreover, this generic difference has been reported in the treatment of PTSD. In fact, CBT (Cognitive Behavioural Therapy) and EMDR (Eye Movement Desensitization and Reprocessing) were more effective in women (Karatzias et al., 2007; Tarrier et al., 2000). Maybe men have a reduced capacity to relive these kinds of experiences. It is likely that remembering more details (what we observed in our results) is related to the capacity of reliving the remembered event. Further experiments are necessary to evaluate if modifying the conditions of the reactivation session can trigger the destabilization/reconsolidation process in men. In experiment 4, we replicated the effect showed in experiment 3 and demonstrated that this effect is likely dependent on the reconsolidation process because the inductor presentation 6 h later, the absence of the reactivation session, or the mere retrieval did not reveal a detrimental effect on autobiographical memories. Altogether, present results strongly suggest that the interference induced by the positive inductor is probably mediated by the reconsolidation process.

To the best of our knowledge, there are only 3 studies on reconsolidation *real-life* autobiographical memories in healthy humans. The first two (Schwabe & Wolf, 2009, 2010) have used the autobiographical memory test (AMT) to reactivate the participants' memories and a story (Schwabe & Wolf, 2009) or stress (Schwabe & Wolf, 2010) as interference. In both, it was found an effect only on neutral memories, suggesting that emotional memories were stronger and that the interference was not effective enough. An alternative interpretation could be that they reactivated all memories at the same time, so it seems difficult to identify on which memory the interference acts. Furthermore, it is impossible to disregard an interplay effect between memories at the retrieval time. The third study (Kredlow & Otto, 2015) found an effect on memories of a tragic event, only when the interference (story) was negative, arguing that when emotional content is the same it is easier to deteriorate the first one, which is different from what we propose. One observation of this work is that the experiment was conducted on the internet and that authors suggested an experimental setting to prove their findings. A final important observation is that none of these studies explored the temporal dynamics of the interference effect on autobiographical memories.

In this work, we meet three control conditions necessary to determinate that the effect on the memory is dependent on reconsolidation (Dudai, 2012; Nader et al., 2000). The first was that only the memory that received the positive interference has interfered. Second, only the reactivated memory was deteriorated. Finally, the inductor did not have an effect when presented out of the reconsolidation window.

The results shown in this study are in agreement with the works that followed a bidirectional (appetitive and aversive) conception of emotions and which dampened a negative memory with a positive experience within a reconsolidation window (Ferrer et al., 2016; Haubrich et al., 2015; Redondo et al., 2014). Furthermore, it is an experimental demonstration of the "integrated memory model" proposed by Lane et al. (2014); in this model, the integration between autobiographical memory, emotion, and the reconsolidation memory is postulated. Lane et al. (2014) proposed a clinical model including the aforementioned components and a comparison among different clinical therapies. In addition, they considered the importance of emotional arousal and the role of semantic structures. Therefore, experimental demonstrations are necessary to determine the validity of the different therapies and mainly the integral model veracity. The importance of this focus on autobiographical memories is crucial because in clinical settings people reactivate these kinds of memories. Additionally, many disorders, for instance, Post Traumatic Stress Disorders (PTSD) and Major Depressive Disorder (MDD) are characterized by a dysfunctional processing of autobiographical memories (Brunet et al., 2008; Köhler et al., 2015). In other words, this model is ecological and appropriate to research in future years.

At present, two alternative groups of treatment, a pharmacological and a non-pharmacological one, are postulated on the reconsolidation field for emotional memories in humans (Dudai, 2012). The pioneers in the first focus (Brunet et al., 2008; Kindt et al., 2009) using propranolol within reconsolidation window managed to dampen a fear memory (traumatic real memory and fear conditioning memory, respectively). After these works, many laboratories have tried to replicate their results in different protocols (for a review, see Agren, 2014). On the other hand, one of the non-pharmacological approaches is a human adaptation from Monfils, Cowansage, Klann, and LeDoux (2009); in this adaptation (Schiller et al., 2010) an extinction essay is presented after memory reactivation, within the reconsolidation window, in a fear conditioned paradigm. This procedure significantly reduced the fear memory. In humans and animals, many groups have replicated the results of this work (Agren, Engman, et al., 2012; Agren, Furmark, Eriksson, & Fredrikson, 2012; Clem & Huganir, 2010; Das, Lawn, & Kamboj, 2015; Flavell, Barber, & Lee, 2011; Oyarzún et al., 2012; Rao-Ruiz et al., 2011; Schiller et al., 2010; Xue et al., 2012) and others have not replicated the effect (Chan, Leung, Westbrook, & McNally, 2010; Costani, Cannas, Sarraulli, Rossi-Arnaud, & Cestari, 2011; Golkar, Bellander, Olsson, & Öhman, 2012; Ishii et al., 2012; Kindt & Soeter, 2013; Pérez-Cuesta & Maldonado, 2009), but actually it is clear that if the memory is properly destabilized in the reactivation session, the phenomenon occurs (Piñeyro, Ferrer Monti, Alfei, Bueno, & Urcelay, 2014). Furthermore, within the non-pharmacological treatments in humans, we proposed to include the interventions that are produced in the interaction between the appetitive and aversive systems (Zhao et al., 2009; and the present work).

To sum up, we demonstrated that after the reactivation of a negative autobiographical memory, the incorporation of positive audio-visual presentation information has detrimental effects on the emotional components of the reactivated memories and that this modification is probably mediated through the reconsolidation process.

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