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The dynamic nature of the reconsolidation process and its boundary conditions: Evidence based on human tests

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ABSTRACT

The reconsolidation process is the mechanism by which the strength and/or content of consolidated memories are updated. This process is triggered by the presentation of a reminder (training cues). It is not always possible to trigger the reconsolidation process. For example, memory age and strength are boundary conditions for the reconsolidation process. Here, we investigated the dynamic changes in these conditions. We propose that the boundary conditions of the reconsolidation process are not fixed and vary as a consequence of the interaction between memory features and reminder characteristics. To modify memory properties, participants received a threatening social protocol that improves memory acquisition or a control condition (fake, without social interaction) prior to learning pairs of meaningless syllables. To determine whether a strong young or old declarative memory undergoes the reconsolidation process, we used an interference task (a second list of pairs of meaningless syllables) to disrupt memory re-stabilization. To assess whether the older memory could be strengthened, we repeated the triggering of reconsolidation. Strong young or old memories modulated by a threatening experience could be interfered during reconsolidation and updated (strengthened) by reconsolidation. Rather than being fixed, boundary conditions vary according to the memory features (strong memory), which indicates the dynamic nature of the reconsolidation process. Our findings demonstrate that it is possible to modify these limits by recruiting the reconsolidation process and making it functionally operative again. This novel scenario opens the possibility to new therapeutically approaches that take into account the reconsolidation process.

1. Introduction

The consolidation model states that memory storage implies a passage from a fragile state to a stable form (McGaugh, 2000). However, following the presentation of a memory cue (reminder), consolidated memories become reactivated, followed by a process of re-stabilization, which is referred to as reconsolidation (Dudai, 2012; Lee, 2009; Nader, Schafe, & Le Doux, 2000). A mismatch or prediction error during reactivation is necessary but not sufficient for the occurrence of reconsolidation (Forcato, Argibay, Pedreira, & Maldonado, 2009; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Sevenster, Beckers, & Kindt, 2013, & Kindt, 2014). Memory features, such as strength and age, are crucial boundary conditions that limit the initiation of the reconsolidation process (Baratti, Boccia, Blake, & Acosta, 2008; Eisenberg & Dudai, 2004; Forcato, Fernandez, & Pedreira, 2013; Inda, Muravieva, & Alberini, 2011; Milekic & Alberini, 2002; Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009). Thus, strong memories are more resistant to reactivation, and consequently, more resistant to interferences (memory strengthening; Dudai & Eisenberg, 2004; Forcato, Fernandez, & Pedreira, 2014; Morris et al., 2006; Suzuki et al., 2004; Taylor, Olausson, Quinn, & Torregrossa, 2009; Wang et al., 2009; Winters, Tucci, & DaCosta-Furtado, 2009). Moreover, reconsolidation is not triggered when the reactivation stimulus is presented at long intervals after training (memory age; Baratti et al., 2008; Eisenberg & Dudai, 2004; Forcato et al., 2013; Inda et al., 2011; Milekic & Alberini, 2002). In summary, it is possible to differentiate the retrieval from the reactivation process considering that

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retrieval only evokes the consolidated memory when it is constrained by the boundary conditions (Forcato et al., 2014; Pedreira et al., 2004).

The reconsolidation process is crucial for the modification of existing memories and is the mechanism by which the strength and/or content of consolidated memories are updated (De Oliveira Alvares et al., 2012, 2013; Forcato, Rodríguez, & Pedreira, 2011; Forcato et al., 2013; Forcato et al., 2014; Inda et al., 2011). Thus, repeated labilization–reconsolidation processes triggered by the presentation of specific reminders increase not only memory precision and persistence but also the resistance to interference during re-stabilization (De Oliveira Alvares et al., 2013; Forcato et al., 2013). Furthermore, the effect of strengthening depends on the age of the memory, in which older memories are more resistant to strengthening (Forcato et al., 2014; Inda et al., 2011).

One topic recurrently considered in reconsolidation studies is the inclusion of the process as the main mechanism to improve therapies for the treatment of anxiety disorders or maladaptive memories (Debiec & Ledoux, 2004; Kindt, Soeter, & Vervliet, 2009; Lee, Di Ciano, Thomas, & Everitt, 2005). The inclusion of this process in novel therapies may represent a crucial change that enables an alternative option in addition to extinction based therapies, which are extensively used in these treatments. The advantage of this change lies in the absence of relapse when extinction is used (Bouton, 2002). However, using these new protocols, it is possible that reconsolidation and extinction are not engaged, and the target fear memory remains in a transitional state (Merlo, Milton, Goozée, Theobald, & Everitt, 2014). Finally, regarding these potential therapies, it is also important to consider that boundary conditions, such as strength, target memory age and the selection of specific parameters in the reactivation process, will be crucial in the design of beneficial therapeutic approaches (Alberini, 2013; Forcato et al., 2013).

Using our declarative memory paradigm (paired associates; Forcato et al., 2007), we have previously demonstrated that the repeated presentation of the reminders cannot labilize or labilize and strengthen an old memory seven days after training. However, the absence of an effect may depend on forgetting, which overshadows memory interference or strengthening (Forcato et al., 2013, 2014). In a recent study (Fernández et al., 2015), we demonstrated how a social threatening event (virtual auditory panel), which was non-specifically related to memory (neutral declarative memory), affects the short- and long-term retention of this neutral declarative memory. In this previous study, we demonstrated that a threatening social situation improves the acquisition and persistence of a strong memory, which prevents the effect of forgetting.

The aim of the present study was to investigate the dynamic changes in the boundary conditions (age and strength) of the reconsolidation process. We proposed that these conditions are not fixed and vary as a consequence of the interaction between memory features and reminder characteristics. We predicted that the changes induced by a threatening social event during an early memory phase modify the memory features, which makes the memory stronger, and creates the possibility to reevaluate the labilization–reconsolidation process under this new condition (Forcato et al., 2013). Thus, we investigated whether a strong young (2 day memory, Experiment 1) or strong old (7 day memory, Experiment 2) declarative memory also undergoes the reconsolidation process and whether it could be strengthened by repeated triggering of the reconsolidation process (Experiment 3). Our findings demonstrate that it is possible to modify these limits by recruiting the reconsolidation process and making it functionally operative again. This possibility of change is relevant for the psychiatric field because it may enable improvements in therapies that use reconsolidation as the main mechanism.

2. Methods and materials

A total of 132 undergraduate and graduate students (77 females and 55 males) from Buenos Aires University (Argentina) participated in the current study. Prior to the experiments, participants provided a written informed consent that was approved by the Ethics Committee of the Review Board of the Sociedad Argentina de Investigación Clínica. The following students were excluded from the experiments: students with cardiovascular and endocrine diseases; students having physical illnesses or being on any kind of medication. Current or lifetime psychopathology or substance abuse was assessed by a clinical psychologist.

2.1. Virtual-auditory panel (VAP) protocol

The VAP protocol (Fernández et al., 2015) is an adaptation of the Trier Social Stress Test (TSST) protocol. The VAP protocol used consisted of three phases (Fig. 1A). *Phase 1* was an undemanding attentional task, in which 16 landscape images were shown and participants were asked to rate the images according to their likes. In *Phase 2*, participants had to prepare a speech to advertise themselves as the best candidate for a professional position; this phase lasted 5 min. Finally, in *Phase 3*, the experimenter explained to the participants that a hospital committee was following the presentation online using a webcam. As in the TSST protocol (Kirschbaum, Pirke, & Hellhammer, 1993), after the presentation, participants had to perform an arithmetic task. The experimenter used a pre-recorded ambient sound (different office sounds such as engines, papers, keys, and chairs) as background and a pitch modifier provided with three different voices (virtual panel) that simulated a hospital committee.

The fake VAP (VAPf) consisted of a non-threatening protocol, similar to the VAP but without the main stress component (Dickerson & Kemeny, 2004). In this case, participants were aware that the task was going to be conducted without social interaction. The first two phases were identical to the previous protocol. In contrast, in *Phase 3*, participants had to write down the speech and to resolve the arithmetic task. We included other tasks such as different multiplications, additions or symbol translations, so both protocols lasted the same time. The virtual panel software and the pre-recorded ambient sound were programmed in Cycling'74. Max/msp 5.0 (Fernández et al., 2015).

2.1.1. Measurements

Baseline measurements for the State Trait Anxiety Inventory (STAI), blood pressure, and heart rate were taken before *Phase 1*, blood pressure and heart rate were measured at four different time points: t0 (before *Phase 1*), t1 (after *Phase 2*), t2 (after the speech presentation) and t3 (after the arithmetic task) (Fig. 1A). Skin conductance level (SCL) was recorded during the entire experiment; we defined the SCL baseline level as the continuous measure during *Phase 1* (Fig. 1A). Blood pressure, heart rate and the STAI were measured for the last time at the end of Phase 3 (Fernández et al., 2015).

2.1.1.1. Subjective rating. Cognitive stress and anxiety were measured using the STAI (Spielberger, Gorsuch, & Lushene, 1970) before and after the administration of the procedures (before Phase 1 and 10 min after Phase 3, respectively).

Blood pressure Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and Heart Rate (HR) were assessed using an Omron HEM 7220 Premium digital Tensiometer (http://omronhealthcare.com/products/7-series-upper-arm-blood-pressure-monitor-bp760). Cardiovascular measurements were taken before Phase 1

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