



Reconsolidation in humans opens up declarative memory to the entrance of new information

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ABSTRACT

A consolidated memory recalled by a reminder enters a vulnerability phase (labilization), followed by a process of stabilization (reconsolidation). Several authors have suggested that the labilization of the consolidated memory makes the incorporation of new information possible. Here, we demonstrate updating in the framework of memory declarative reconsolidation in humans by giving an opportune verbal instruction. Volunteers learn an association between five cue-syllables (L1) and their respective response-syllables. Twenty-four hours later, the paired-associate verbal memory is labilized by exposing the subjects to the reminder, and then they receive the verbal instruction of adding three new cue-response syllables (INFO) with their respective responses to the former list of five. The new information is incorporated into the single former L1-memory and both INFO and L1 are successfully retrieved on the third day. However, when the instruction is not preceded by a proper reminder, or when the instruction omits the order of adding the INFO into the former L1-memory, we observed interference in retrieval of both the original and the new information, suggesting that they are encoded independently and coexist as separate memories.

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1. Introduction

According to the reconsolidation hypothesis, consolidated memory recalled by a reminder enters a vulnerability phase (labilization) during which it is transiently sensitive to disruption (or enhancement), followed by a process of stabilization that returns memory to the former state (Nader, Schafe, & LeDoux, 2000; Sara, 2000a). The reminder is the event that triggers the labilization–reconsolidation process of the memory. This process has been shown in very diverse species and types of memory, including the human procedural memory of a motor skill task (Walker, Brakefield, Hobson, & Stickgold, 2003), and reconsolidation in verbal learning (Forcato, Burgos, Argibay, Pedreira, and Maldonado, 2007). In both cases, the amnesic agent was other learning and recently, Kindt, Soeter, and Vervliet (2009) showed that oral administration of the β -adrenergic receptor antagonist propranolol disrupts the human labilization–reconsolidation process of a fear memory, erasing its behavioural expression 24 h later and preventing the return of fear.

Since the early formulation of the reconsolidation hypothesis, several controversial items have arisen, mainly concerning the

dubious functionality of positing a consolidated memory in the transient but risky stage of being labilized. Several authors proposed that retrieval triggers a reconsolidation process that allows the integration of new information into the background of the past (memory updating). In other words, reconsolidation would make it possible to associate new learning with already established and reactivated memories (Lewis, 1979; Nader et al., 2000; Sara, 2000b). Indeed, it seems intuitively obvious that memory needs to be continuously updated with new learning (Alberini, 2007) and some authors have studied memory updating in the framework of reconsolidation (Hupbach, Gomez, Hardt, & Nadel, 2007; Morris et al., 2006; Rodriguez-Ortiz, De la Cruz, Gutierrez, & Bermudez-Rattoni, 2005; Tronel, Milekic, & Alberini, 2005).

In our first paper on reconsolidation with humans (Forcato et al., 2007) we highlighted the suitability of this model to study the role of reconsolidation in memory updating thanks to the option of using a verbal instruction as a tool in the experiment. In the present paper, we address the possibility that a proper verbal instruction, given contingently upon a memory that has just been labilized by a reminder, allows us to add new information to the former memory.

Based on the results of our previous papers (Forcato, Argibay, Pedreira, & Maldonado, 2009; Forcato et al., 2007), the present research was aimed at studying the effect of changing either the

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parametrical conditions of the reminder or the type of verbal instruction on the updating process, in the framework of human reconsolidation.

Here, we perform a series of experiments in which volunteers learn on the first day an association between five cue-syllables and their respective response-syllables (List 1, L1). On the second day, the paired-associate verbal memory is labilized by exposing the subjects to the reminder, and then they receive the verbal Instruction of adding three new pairs of cue-response syllables (INFO) to the former list of five. The new information is incorporated into the single former L1-memory and both INFO and L1 are successfully retrieved on the third day. However, when the Instruction is not preceded by a proper reminder, or the instruction omits the order of adding the INFO to the former L1-memory, the new information is encoded in a new INFO-memory that coexists with the previous L1-memory. This co-existence produces the simultaneous recruitment of related information at retrieval, and consequently the evocation of either of the two memories interferes with the expression of the other (retrieval interference, Forcato et al., 2007, 2009; McGeoch, 1932; Greene, 1992) which brings about a poor recall of both INFO and L1. Therefore, we show the addition of new information into the former memory occurs one day after acquisition provided the information is given immediately after the reminder that triggers reconsolidation and the Instruction includes the order of adding the INFO-pairs in the L1-memory.

2. Materials and methods

2.1. Subjects

109 healthy undergraduate and graduate students from Buenos Aires University volunteered for the study. Of these, 21 participants were excluded from the data analysis because they did not reach the inclusion criteria. Their ages ranged from 20 to 35, with a mean of 25 (31 men, 57 women). Each participant was randomly assigned to one of eight groups. All participants provided written informed consent that had been approved by the Comité de Ética de la Sociedad Argentina de Investigación Clínica Review Board.

2.2. Inclusion criteria

Subjects with at least 65% of correct responses in the last four training trials (13/20 correct responses) were included in the data analysis.

2.3. Experimental room and experimental protocol

Experiments took place in a dark room and were conducted using a personal computer. Each subject was provided with ear-

phones and seated facing a monitor placed in front of a large screen on the back wall (Forcato et al., 2007, 2009).

Each three-day experiment consisted of a training session (Day 1), a treatment session (Day 2) and a testing session (Day 3). Eight distinct groups of volunteers were formed: four main groups and four control groups. The four main groups were the Reminder-Group, the No-reminder-Group, the Fake-reminder-Group and the No-instruction-Group. The four control groups were the Reminder-Control, the No-reminder-Control, the Fake-reminder-Control and the No-instruction-Control (Table 1).

2.4. The four main groups

2.4.1. The Reminder-group (n = 12)

2.4.1.1. The training session (Day 1). Each training trial (Fig. 1A.1) was comprised of a first period during which the context was formed (**the context period**), followed by a second during which a series of nonsense-syllables were presented as paired-associates (**the syllable period**). The context period consisted of a fixed sequence of three accumulative steps: a first step of a red light projected on the large screen for 2 s, a second step of the same light plus an image of a forest in autumn on the monitor screen for 2 s, and a third step of the light plus the image plus classical music coming through the earphones for 4-s. This specific context persisted during the syllable presentation. The syllable period that followed the former started with the presentation of a cue-syllable on the left-hand side of the monitor screen and an empty response-box on the right-hand side. Each cue-syllable was taken at random from a list of five pairs. Subjects were given 5 s to write the corresponding response-syllable. Once that period had finished, three situations were possible: first, if no syllable was written, the correct one was shown for 4 s; second, if an incorrect syllable was written, it was replaced by the correct one and it was shown for 4 s; and third, if the correct response was given, it stayed for 4 s longer. Immediately after that, another cue-syllable was shown and the process was repeated until the list was over. Altogether a trial lasted 53 s (8 s for context period and 45 s for syllable presentation). Throughout this experiment, every time a subject faced a cue-syllable and wrote down an erroneous response or no response an error was computed. The **training** consisted of the presentation of 10 trials, separated by a 4-s intertrial interval. In the first training trial, the list 1 (L1) was shown, and in the successive trials subjects were required to write down the corresponding response-syllable for each cue-syllable presented. L1 was composed of five pairs of nonsense cue-response-syllables in Spanish: **ITE**-OBN, **ASP**-UOD, **FLI**-AIO, **NEB**-FOT, **COS**-GLE (bold type: cue-syllable; regular type: response-syllable) (Fig. 1A.2). Subjects that failed to obtain 65% (13/20) of correct responses in the last four trials were excluded (Forcato et al., 2007, 2009). The training session lasted 10 min.

Table 1

Experimental Groups. L1-training stands for the L1-training received on Day 1, Instruction for the instruction to incorporate the new syllable-pairs into the L1-memory, No-instruction stands for an instruction without the order of incorporating INFO in the L1-memory, R for the reminder, R_{fake} for the fake-reminder, INFO for the info trial (specific context plus three new pair of syllables), INFO + L1-testing for the evaluation of the eight pairs of syllables (5 L1 + 3 INFO) presented at random order and L1-testing for the evaluation of the 5 L1-pairs.

	Groups	Day 1	Day 2	Day 3
Main groups	Reminder-Group	L1-training	R__Instruction__INFO	L1 + INFO-testing
	No-reminder-Group	L1-training	Instruction__INFO	L1 + INFO-testing
	Fake-reminder-Group	L1-training	R _{fake} __Instruction__INFO	L1 + INFO-testing
	No-instruction-Group	L1-training	R__No-instruction__INFO	L1 + INFO-testing
Control groups	Reminder-Control	L1-training	R	L1-testing
	No-reminder-Control	L1-training	Instruction__INFO	L1-testing
	Fake-reminder-Control	L1-training	R _{fake} __Instruction__INFO	L1-testing
	No-instruction-Control	L1-training	R__No-instruction__INFO	L1-testing

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