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Review Paper

Memory beyond expression

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This review is dedicated in honor of Professor Héctor Maldonado.

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ABSTRACT

The idea that memories are not invariable after the consolidation process has led to new perspectives about several mnemonic processes. In this framework, we review our studies on the modulation of memory expression during reconsolidation. We propose that during both memory consolidation and reconsolidation, neuromodulators can determine the probability of the memory trace to guide behavior, i.e. they can either increase or decrease its behavioral expressibility without affecting the potential of persistent memories to be activated and become labile. Our hypothesis is based on the findings that positive modulation of memory expression during reconsolidation occurs even if memories are behaviorally unexpressed. This review discusses the original approach taken in the studies of the crab *Neohelice* (*Chasmagnathus*) *granulata*, which was then successfully applied to test the hypothesis in rodent fear memory. Data presented offers a new way of thinking about both weak trainings and experimental amnesia: memory retrieval can be dissociated from memory expression. Furthermore, the strategy presented here allowed us to show in human declarative memory that the periods in which long-term memory can be activated and become labile during reconsolidation exceeds the periods in which that memory is expressed, providing direct evidence that conscious access to memory is not needed for reconsolidation. Specific controls based on the constraints of reminders to trigger reconsolidation allow us to distinguish between obliterated and unexpressed but activated long-term memories after amnesic treatments, weak trainings and forgetting. In the hypothesis discussed, memory expressibility – the outcome of experience-dependent changes in the potential to behave – is considered as a flexible and modulable attribute of long-term memories. Expression seems to be just one of the possible fates of re-activated memories.

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1. Introduction

How do we select from recent experiences those that will be stored as memories in the long term? The theory of the endogenous modulation of memory consolidation posits that – during the process by which a memory turns from short term into long term – neuromodulatory systems activated by relevant experiences modulate the storage of long-term memory (LTM) (McGaugh, 1989). The experimental approaches that have guided much of the research on the cellular and systemic mechanisms of memory have been based on an operational definition of memory: a change in behavior as a result of previous experience. However, recent studies concerning the action of neuromodulators during memory reconsolidation (Frenkel et al., 2005a) have led us to rethink certain central notions: can unexpressed memories be re-activated and become labile again? Are memory expression and memory reactivation dissociable processes? Are retrieval and memory expression interchangeable concepts?

1.1. Reconsolidation hypothesis

The reconsolidation hypothesis proposes that a previously consolidated memory can enter an unstable state when recalled (memory labilization), becoming transiently sensitive again to disruption by interfering agents (Lewis, 1979; Misanin et al., 1968; Przybyslawski and Sara, 1997; Sara, 2000). Today, the cumulative evidence based on hundreds of studies on reconsolidation challenges once more the traditional view of memory consolidation, principally the notion that new memories are fixed after being consolidated (Dudai, 2012; Nader and Einarsson, 2010; Reichelt and Lee, 2013). This new view has led to novel perspectives about several mnemonic processes (Alberini et al., 2013; Baratti et al., 2009; Dudai and Eisenberg, 2004; Dudai and Morris, 2013; Frenkel et al., 2010b; Gold, 2006; Hupbach et al., 2007; Nader and Wang, 2006; Sara and Hars, 2006; Sierra et al., 2013). In this framework, we review our studies on the positive modulation of memory expression during reconsolidation. Hereafter, the term "memory expression" is referred to as the expression of a representation in behavior (Schacter, 2007).

1.2. Reconsolidation and memory enhancing effects

Although most reconsolidation studies have shown that memory can be disrupted by interfering agents during this phase, memory retention can be increased during reconsolidation by enhancing agents, multiple reactivation sessions and real-life events (Alberini, 2007, 2011; Dudai, 2009; Gordon and Spear, 1973; Lee, 2008; Lewis, 1976; Rodriguez et al., 1999, 1993; Rovee-Collier et al., 1980). Among the earliest studies that reported an enhancing effect specifically during reconsolidation was one in our laboratory with the crab *Chasmagnathus*, now formally known as the *Neohelice*, *granulata* memory model (Frenkel et al., 2005a).

Here we review our studies that have highlighted that memory re-activation, but not memory expression, of a consolidated trace is necessary for the emergence of reconsolidation. We will discuss results showing that the periods in which a consolidated LTM can be activated and become labile exceed the periods in which that memory trace is expressed in behavior. In fact, new studies support the view that mechanisms mediating memory re-activation and behavioral expression of memory can indeed be dissociated.

Two other terms require clarification before continuing: 'persistence' and '(re)activation'. The term persistence (an "alternative term has been commonly used, 'storage', which is a misguided metaphor, of the type quite abundant in the science of memory": page 191 in Roediger et al. (2007)) here refers to the retention over time of the information learned; an experience-dependent internal representation or acquired model of the world, that is only, and only sometimes, expressed in overt behavior (Dudai, 2002b; Eichenbaum, 2007; Roediger et al., 2007). In addition, for the term memory reactivation, we hereafter refer to it as the activation concept, agreeing with Lewis (1979): "Active memory is a subset of inactive memories and contains either newly formed memories or established retrieved memories or both."

1.3. Reminder environment to induce reconsolidation: the mismatch component

A crucial issue to comprehend the role of reconsolidation is to know the boundary conditions necessary to induce this process (Dudai, 2012; Nader and Einarsson, 2010; Pedreira and Romano, 2013). The duration of the reminder, which should be limited to induce reconsolidation and not extinction (Dudai, 2012; Eisenberg and Dudai, 2004; Pedreira and Maldonado, 2003), is a notable one. Outstandingly, the mismatch requirement is another essential boundary condition to understand the reconsolidation process itself and to elaborate the present discussion. The mismatch component covers the concept of prediction error that arises from discrepancy theories of associative learning (Rescorla and Wagner, 1972); the mismatch between the predicted unconditioned stimulus and the actual unconditioned stimulus is a key condition to generate new learning. Today, it is not surprising that the labilization–reconsolidation process is also triggered by a rupture of the expectations generated by the activated representation of the experience, as was originally demonstrated in *Chasmagnathus* memory model and then in humans by Professor Maldonado's laboratory (Forcato et al., 2009; Pedreira et al., 2004). In accordance with the general principles of memory organization throughout evolution (Barco et al., 2006; Carew and Sutton, 2001), this boundary condition has been confirmed in several species (Diaz-Mataix et al., 2013; Dudai, 2006, 2009; Forcato et al., 2009; Frenkel et al., 2005a; Morris et al., 2006; Nader et al., 2000; Pedreira et al., 2004; Pedreira and Romano, 2013; Perez-Cuesta and Maldonado, 2009; Rossato et al., 2007; Sevenster et al., 2012, 2013; Winters et al., 2009). To illustrate the point, the effects of some amnesic agents administered after LTM activation will not take place if the brief context presentation is reinforced (i.e. no mismatch condition at reminder session) by the presentation of one training trial at the end of the reminder session in *Chasmagnathus* (Pedreira et al., 2004; Pedreira and Romano, 2013). In consequence, reminder

presentation is not a sufficient condition to induce reconsolidation, mismatch needs to take place between what is expected in a given situation and what actually occurs. The confirmation of this boundary condition was central to put forward the original idea that reconsolidation initiates a period of lability in which the original memory is open for update (Alberini et al., 2013; Dudai, 2012; Nader et al., 2000; Sara, 2000). In brief, like associative learning, strong evidence supports the view that reconsolidation depends on detecting mismatches between actual and expected experiences during the reminder session.

1.4. Intersection between experimental amnesias and reconsolidation

The hypothesis is based on the findings that positive modulation of memory expression during reconsolidation occurs even if memories are unexpressed. Perceptibly, some of the studies revised here touch very closely on the traditional and long-standing debate concerning experimental amnesias because several treatments or conditions can reveal memories that otherwise remain veiled. Latent memory, overshadowing and blocking are common features of learning and memory processes that were widely demonstrated across the animal kingdom, as well as in many studies that showed recovery of experimental amnesias (Cahill et al., 2001; Gold, 2006; Gold and King, 1974; Haycock and McGaugh, 1973; Lewis, 1976, 1979; Nader and Wang, 2006; Parvez et al., 2005; Philips et al., 2006; Urcelay and Miller, 2008). These recoveries are at the heart of the ongoing debate about the nature of experimental amnesia: whether amnesic treatments interfere with those events taking place during memory consolidation or whether these treatments interfere with the retrieval process of memories that were effectively formed (de Hoz et al., 2004; Hardt et al., 2009; Miller and Matzel, 2006; Nader and Wang, 2006; Rescorla, 1988; Squire, 2006) (see special section The Neurobiology of Amnesia in Learn Mem, vol. 13, issue 5, 2006). Classical strategies to recover memory from experimental amnesia include exposing amnesic animals to, for example, reminders, or either unconditioned or conditioned stimuli. In the memory "storage" deficit view, sub-threshold memories, which might remain after the administration of amnesic agents during consolidation, could be added to the new memories formed during the subsequent reminder sessions. Consequently, two memories (the original one plus that formed when animals are exposed to a reminder, for instance), which separately cannot be operationally noticed in the performance at testing, can be synergistically added – summation – and thus induce the expected change in behavior at testing (Gold et al., 1973; Squire, 2006). Accordingly, these "reminder effects" had been traditionally explained by processes other than memory updating.

On the other hand, the classical alternative explanation is that the memory that was impaired during consolidation is present, was formed, but cannot be retrieved (Brioni et al., 1989; Gold, 2006; Hardt et al., 2009; Miller and Matzel, 2006; Nader and Wang, 2006). The view proposes that during consolidation retrieval links are formed. These links are pharmacologically disrupted by the amnesic agents, resulting in dysfunctional retrieval links that can, however, become functional under certain situations (like modulation of retrieval by drugs and state dependent phenomena).

These antagonistic views on the question of storage versus retrieval deficit are a simplification of a vast literature that has been repeatedly discussed and is not the objective of this paper to fully revise. In fact, some authors consider that memory traces change over time and, eventually, spontaneous reactivation and late consolidation processes can explain memory recovery after experimental amnesias (Amaral et al., 2008; Cahill et al., 2001). In this complex context, reconsolidation studies may have much to offer regarding the nature of experimental amnesias (Gold, 2006; Riccio et al., 2006; Sara and Hars, 2006). Key features in the hypothesis presented would add a different interpretation for experimental amnesia, mainly because the memory enhancing effects here discussed specifically belong to the reconsolidation process.

2. The context-signal memory model in the crab *Chasmagnathus*

Crustaceans are traditionally used for neurobiological studies in memory. The *Neohelice* memory model is based on the escape response of the crab *Chasmagnathus* to the attacks of its aerial predators, where crabs associate the training context with a visual danger stimulus (VDS) passing overhead (reviewed in detail (Tomsic and Romano, 2013)). After the iterative spaced presentation of the VDS, a strong freezing-to-VDS response replaces the initial escape response (Maldonado, 2002). A strong training protocol consists of fifteen spaced (180 s) trials (each trial of 9 s duration, two VDS presentations). Following this strong training protocol, crabs exhibit LTM from 24 up to 96 h later (Fig. 1A). Since the memory under study arises as a consequence of an association between the context, (the conditioned stimulus, CS), and the VDS (the unconditioned stimulus, US), it is termed context-signal memory (CSM; Maldonado, 2002). CSM expression is revealed at testing sessions as a significant decrease in locomotor activity when the VDS is presented. This decrease in activity is due to an increase in the number of animals displaying a freezing response instead of escaping (Maldonado, 2002; Pereyra et al., 2000). Typical experimental protocols involve pair groups of crabs, where each pair has trained crabs that receive US presentations and belong to the trained group, and untrained crabs which belong to the untrained group (Fig. 1A, Caffaro et al., 2012; Tomsic and Romano, 2013).

Studies investigating the mechanisms underlying the different memory phases have shown that CSM consolidation, extinction and reconsolidation process can be blocked by, for instance, protein and mRNA synthesis inhibitors, *N*-methyl-D-aspartic acid (NMDA)-like glutamatergic and muscarinic cholinergic receptors antagonist; and enhanced by, for instance, angiotensins or biogenic amines (Pedreira and Romano, 2013; Tomsic and Romano, 2013). In addition, a training protocol has also been developed for contextual Pavlovian conditioning (Fustinana et al., 2013). Some neurons involved in CSM have been studied (Tomsic et al., 2009) while at the molecular level it has been demonstrated that some kinase pathways and the NFκ-B transcription factor are crucial for the emergence of CSM processes (Romano et al., 2006; Tomsic and Romano, 2013).

2.1. Our previous view: weak training only induces short-term memory in crabs; neuromodulators can turn short-term into long-term memory

Not all events from recent experiences are stored in memory. From the canonical point of view, a key role in the selection of the events to be remembered is played by the systems that modulate memory consolidation. The experience activates endogenous processes (for instance, stress hormones activated by a traumatic event) that will modulate memory strength (McGaugh, 2000; McGaugh and Roozendaal, 2009). A traditional strategy to study modulators in memory research is to decrease either the intensity or the number of trials during training, which induces only short-term memory, lasting for a few hours after training (Stough et al., 2006). In the *Neohelice*, weakly trained crabs (6 instead of 15 trials) do display short-term (4 h) but not long-term memory (Smal et al., 2011) (Fig. 1B). This short-term memory can be turned into LTM by the action of, for instance, neuromodulators and kinase activators

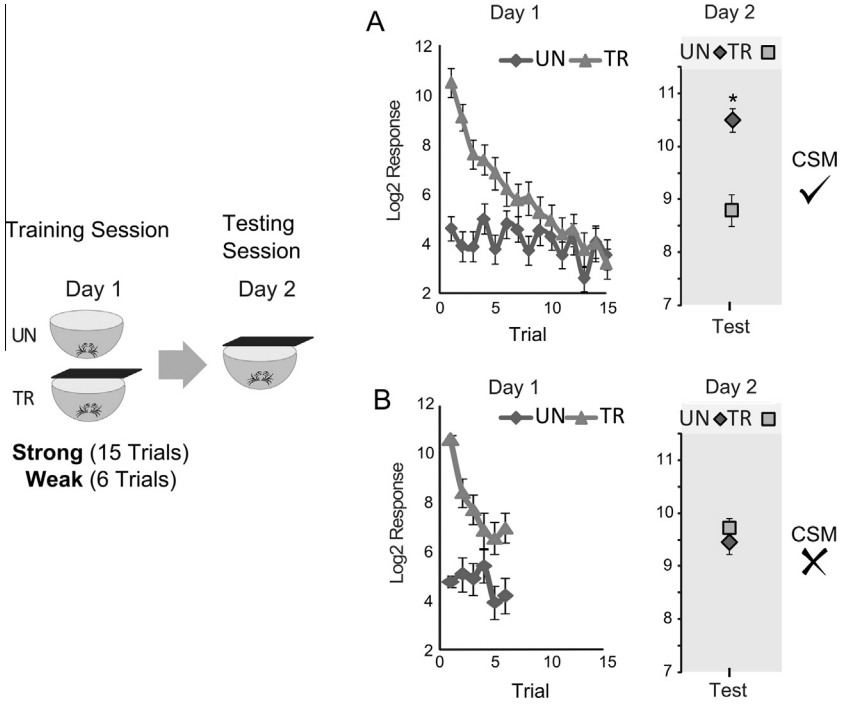

Fig. 1. *Neohelice* (*Chasmagnathus*) *granulata* memory paradigm. Behavioral experiments are conducted in an actometer consisting of a bowl connected to a transducer device. The visual danger stimulus (VDS) consists of the horizontal displacement, 90 degrees back and forth twice, of a black rectangular screen. (A) Strong Training Session (15 trials; ITI = 171 s) induces a long LTM (CSM, context signal memory) that is behaviorally disclosed as a decrease in escape response of the trained (TR) group compared with an Untrained (UN) group in testing sessions (Day 2). (B) Weak Training Session (6 trials) induces a memory that is expressed until 4 h after training, but not after 8 h. Graphs ordinates: log2 (data log2 transformed) trial scores during VDS presentation (means ± SE). * Indicate statistical differences between TR and UN groups described in the respective study.

(Delorenzi et al., 1995; Romano et al., 1996; Tomsic and Romano, 2013). This protocol has been regularly used to test several enhancing effects (Delorenzi et al., 1996; Romano et al., 1996; Smal et al., 2011) during consolidation and retrieval (Carbo Tano et al., 2009; Delorenzi et al., 2000, 1996, 1995; Delorenzi and Maldonado, 1999; Frenkel et al., 2002, 2005a,b; Kaczer and Maldonado, 2009; Romano et al., 1996).

Initial studies in the euryhaline, semiterrestrial and powerful osmoregulator crab *Chasmagnathus* showed that endogenous angiotensins, specifically angiotensin II, appeared early in evolution as a functional link between water shortage and behavioral adaptations, including the improvement of memory (Delorenzi et al., 2000, 1996, 1995; Delorenzi and Maldonado, 1999; Frenkel et al., 2010a, 2002, 2005a,b; Frenkel et al., 2010b). The studies are in agreement with the hypothesis that, when animals cope with water shortages, the angiotensinergic system activates coordinated actions, from osmoregulation to behavior, which, as a whole, enable the animal to survive under this ethological challenge (De Mello, 2014; Maren et al., 1994; Wright et al., 2002). Specifically, when crabs are water-deprived for 2 h an increase in brain angiotensin II improves both memory consolidation and retrieval processes.

2.2. A function of reconsolidation: a change in memory strength by the influence of a concurrent experience

In another attempt to shed light on the functional value of reconsolidation, our earlier studies explored the possibility that concurrent real-life experiences can improve memory reconsolidation in crabs (Frenkel et al., 2005a).

In crabs, when the memory generated by a strong training is activated by a brief (5 min) context presentation 24–48 h after training, reconsolidation is triggered. During this period, the CSM is transiently susceptible to, for instance, protein synthesis inhibition, to *N*-methyl-D-aspartate receptor antagonist, and to the inhibition of transcription factor NF-kappaB (Pedreira and Maldonado, 2003; Pedreira and Romano, 2013). Exploring a putative reconsolidation improvement by concurrent experiences, we show that memory reactivation *per se* does not improve memory retention after weak training, but a 2-h episode of water deprivation, concurrent upon reconsolidation, improves memory, resulting in crabs that show LTM (Frenkel et al., 2005a). Such concurrency between water deprivation and reconsolidation is necessary to achieve memory enhancement. The improvement was not revealed when: (1) memory had not been activated because a novel context was presented in the reminder session; (2) the rise in brain angiotensin II occurred late during the reconsolidation process (water deprivation delayed 6 h after reminder exposure); and (3) the reconsolidation process was disrupted by a protein synthesis inhibitor. Processes other than memory update (1.4) can explain several reminder effects. However, the constraints of reminders for triggering reconsolidation (mismatch condition (1.3)) allow us to unveil unexpressed but activated LTM.

2.3. Weak training induces LTM: angiotensin modulates long-term memory expression but not memory persistence

The reminder is not sufficient to induce reconsolidation, and a mismatch needs to take place between what is expected in a given situation and what actually occurs, to initiate the reconsolidation process (1.3). Fig. 2 shows one crucial experiment in the study of reconsolidation where it was shown, for the first time, that a real life episode enhances memory specifically during reconsolidation. The reminder presentation is not sufficient to attain memory improvement: the parametric condition of mismatch needs to take place (Frenkel et al., 2005a). After weak training, even when

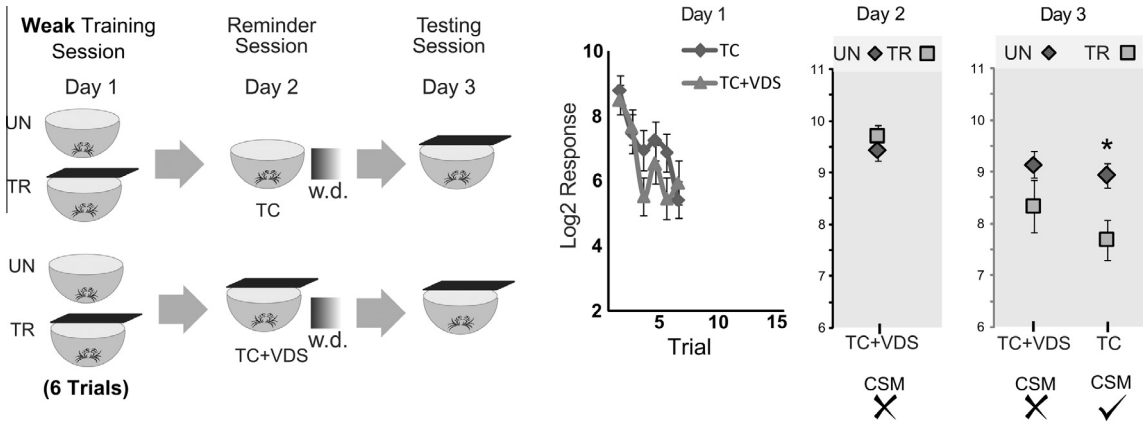

Fig. 2. A mismatch is required to enhance CSM during reconsolidation. On Day 1 animals were trained with a Weak Training Session. On Day 2, *Reminder Session*. Unreinforced reminder: groups were re-exposed to the training context for 5 min (this procedure activates and initiates memory reconsolidation). Reinforced reminder: groups were re-exposed to the training context for 5 min and at the end received a single VDS presentation (this reminder does not trigger the reconsolidation process). Next, all animals were water deprived for 2 h in their individual resting containers. *Testing Session* (Day 3): memory expression was disclosed for the unreinforced reminder group, but not for animals that were exposed to the reinforced reminder. TC: training context. Symbols as in Fig. 1. Adapted from Frenkel et al. (2005a).

memory expression is not observed in the long term, reconsolidation can be triggered on the condition that the presentation of the training context is non-reinforced at the reminder sessions. Thus, although the animals do not express the freezing behavior in the long term, the memory – the association between the training context and the VDS, the acquired model of the world – persists and is activated. The important issue here is that the mismatch is necessary to reinstate the freezing response – memory expression – in subsequent testing. The mismatch condition requires the termination of the reminder re-exposure without the predicted reinforcement. The reinforced reminder (re-exposure to the training context plus VDS presentation; Fig. 2) impedes the improving effect of water deprivation that modifies CSM expression, even when this reminder includes more training cues than those presented during the reminder that actually triggers the reconsolidation process (Frenkel et al., 2005a). In short, the mismatch component of the reminder session, via the activated (and unexpressed) memory trace, was indeed detected.

This study, early evidence that memory can be positively modulated during reconsolidation through an identified endogenous process triggered during a real-life episode, represented an important step toward supporting the reconsolidation hypothesis (Alberini, 2007; Dudai, 2009). So again, the question is whether long-term expression is required in order for a LTM to be activated and become labile. At that time, cumulative evidence led us to a new interpretation of both the long-term existence of the CSM generated by weak training protocols and the long-term nature of the mnesic angiotensin actions. Results summarized in Table 1

Table 1
Select results showing that angiotensin II modulates LTM expression but not memory persistence in *Neohelice*. *Symbols:* water deprivation (w.d.) and angiotensin II (ANGII) effects on different CSM phases; SAR (ANGII antagonist); remind.sess. (reminder session regarding reconsolidation studies); VDS (Visual Danger Stimulus, the reinforcement); CHX (cycloheximide); AMD received actinomycin D; (+) denotes long-term memory expression; (–) denotes no long-term memory expression. [1] (Delorenzi et al., 1997, 1996, 1995; Delorenzi and Maldonado, 1999); [2] (Frenkel et al., 2010a, 2002); [3] (Frenkel et al., 2005b); [4] (Frenkel et al., 2005a); [5] (Frenkel et al., 2010b).

		Treatment on					
Training		Consolidation		Retrieval [3]		Reconsolidation [4,5]	
	CSM		CSM		CSM		CSM
Weak Training (WTP)	–			w.d.	+	remind.sess.	–
		w.d. [2]	+	w.d. plus SAR	–	remind.sess. plus VDS	–
		w.d. plus SAR [2]	–	ANGII	+	remind.sess. plus w.d.	+
		ANGII [1]	+	ANGII plus SAR	–	novel context plus w.d.	–
		ANGII plus SAR [1]	–			remind.sess. plus ANGII	+
						remind.sess. plus VDS and w.d.	–
						remind.sess. plus VDS and ANGII	–
						remind.sess. plus w.d. and CHX	–
						remind.sess. plus w.d. and SAR	–
		SAR	w.d. [3]	+			
		CHX	w.d. [3]	–			
		AMD	w.d. [3]	–			
Strong Training (STP)	+	SAR [1]	–				
						remind.sess.	+
						remind.sess. plus SAR	–
						remind.sess. plus VDS and SAR	+
		SAR				remind.sess. plus w.d.	
		CHX				remind.sess. plus w.d.	+
							–
		SAR				novel context plus w.d.	–
		SAR				remind.sess. plus VDS	–

demonstrated that weak training resulted in an unexpressed LTM. Weakly trained crabs can reveal long-term CSM if enhanced during reconsolidation, which necessarily entails activating memory, evaluating the mismatch component of the reminder and then, memory becoming labile. Besides, reconsolidation needs to be contingent upon a memory enhancing episode (2 h of water deprivation) (Table 1) (Frenkel et al., 2005a, 2010b) or with pharmacological interventions that improve CSM (Carbo Tano et al., 2009). Therefore, weak training protocols do build a LTM that can be activated but do not gain appreciable control over behavior at testing. Memory activation is necessary to both evaluate the mismatch condition of the reminder and induce the post-reminder state of malleability (Fig. 3). Remarkably, this unexpressed LTM is dependent on new protein synthesis or new mRNA transcription after acquisition (Table 1) (Frenkel et al., 2010b), definite neurobiological characteristics of LTM (Alberini, 2009; Davis and Squire, 1984; Stough et al., 2006), but see (Gold, 2008b; Sadowski et al., 2011).

With these results, our conception of the long-term nature of the mnemonic angiotensin actions necessarily changes. Angiotensin II receptors antagonist Saralasin is a consistent amnesic agent used in *Chasmagnathus* during both consolidation and reconsolidation (Delorenzi and Maldonado, 1999; Delorenzi et al., 1996; Frenkel et al., 2005a). However, strongly trained, saralasin-treated animals do build an unexpressed LTM, similar to those built by weak training (Frenkel et al., 2010b) (Table 1). Unlike cycloheximide administration – where crabs fail to recover expression – the saralasin amnesic retrograde effects are best explained as a negative interference of the expression of the LTM. Saralasin-treated animals do build and consolidate a LTM trace which can be activated, but it does not gain appreciable control over behavior (Table 1) (Frenkel et al., 2010b). Overall, the results strongly suggest that in *Chasmagnathus* angiotensin II is a neuromodulator that during consolidation and reconsolidation determines whether the activated memory trace will guide behavior, increasing its long-term expression, but not its persistence. Under the evaluated parametric condition of our studies, both the persistence and the potential to be activated in the long term are independent of the neuromodulator angiotensin II.

This view contrasts with our first explanation of the mnesic nature of angiotensins on CSM which was consistent with the concept that memory modulatory systems are endogenous systems that influence memory storage processes (Braszko et al., 2006; Delorenzi et al., 2000, 1997, 1996, 1995; Delorenzi and Maldonado, 1999; Frenkel et al., 2002; Khoury et al., 2012; Wright et al., 2008).

Results presented before are consistent with the view that long-term CSM traces can persist, be activated and become labile without being behaviorally expressed. Memory improvements during reconsolidation may point toward a proposed function of the reconsolidation process associated with reinforcing items that are critical for the retrieval process (Dudai and Eisenberg, 2004). It is possible that reconsolidation reflects a process that allows memory re-evaluation, changing the hierarchy of the memories that can potentially control behavior.

Certainly, these results could be seen as part of the vast number of studies that have shown that a treatment or condition may reveal a memory that otherwise remains unexpressed (Cahill et al., 2001; Gold et al., 1973; Haycock et al., 1973; Nader and Wang, 2006; Parvez et al., 2005; Philips et al., 2006; Rescorla, 1988; Riccio et al., 2006; Rovee-Collier et al., 1980). However,

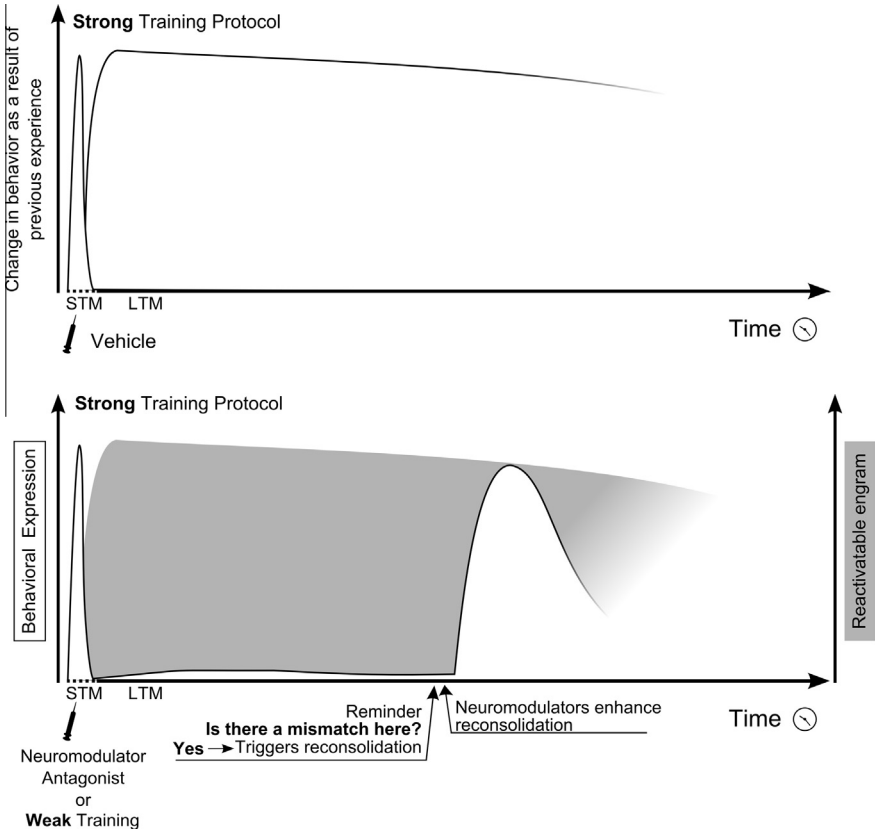

Fig. 3. Proposed model after weak training or the action of amnesic agents based on neuromodulator action: long-term CSM trace can persist, be activated and become labile without behavioral expression. Above, the standard CSM dynamics model. Below, CSM behavioral expression (white) and CSM activatable engram (gray) are shown. Here, an activatable engram is, indeed, induced by a weak training protocol (Section 2), or also after the neuromodulator antagonism following a strong training protocol (Sections 2 and 3), although no behavioral expression is disclosed. However, memory can gain behavioral expression again if a positive modulation occurs during a reconsolidation process. The mismatch condition during the remainder session is a necessary condition to trigger reconsolidation.

several features in the present approach are different from and contrast with canonical interpretations that are discussed, in the next section, in light of the effects of the amnesic agent scopolamine on CSM.

3. A modulable and flexible attribute of LTM expression: implications for the question of the nature of experimental amnesia

3.1. Chasmagnathus

The muscarinic antagonist scopolamine has amnesic properties that have led to its widespread use to induce impairments in learning and memory in both vertebrate and invertebrate memory models, crabs included (Baratti et al., 2009; Beron de Astrada and Maldonado, 1999; Buccafusco, 2009; da Silva et al., 2009; Quirarte et al., 1994; Weinberger, 2006). At this point, it is straightforward to envisage our working hypothesis: the amnesic effect of scopolamine is due to disruption of LTM expression rather than interference in the mechanism of memory persistence or failure in retrieval mechanisms. Fig. 4 shows a crucial result of such a study (Caffaro et al., 2012). Consequently, after scopolamine administration there is a persistent memory trace that is not expressed in the long term, but can be activated and labilized by appropriate reminders. Table 2 summarizes the results showing that the change in performance after a reminder is due to enhancement of the expression of a reconsolidated memory trace, but not to other processes such as summation of a residual memory trace with additional learning produced during the reminder presentation (Gold, 2006; Gold et al., 1973). The necessities for a reminder which occurs within a particular temporal window after memory reactivation are classical controls for reconsolidation (Dudai, 2009; Dudai and Eisenberg, 2004; Nader and Einarsson, 2010). However, these classical controls cannot fully reject that a new learning process is taking place, which could explain the recovery of memory expression observed at testing (a new learning, for instance) (1.4). In this sense, several studies are concerned with these recoveries, observing that the complete removal of memory is not yet demonstrable and alternative views should not be discarded (Cahill et al., 2001; Hardt et al., 2009; Lewis, 1976). Moreover, this difficulty gets worse in the case of post-retrieval, post-activation improvement. For example, sub-threshold memories could be added to new memories formed concomitantly with the reminder, or can be synergistically added (“summation”) and thus induce memory expression at testing (Gold et al., 1973a). Several approaches that were able to recover memory from experimental amnesias might be considered as new learning added onto a residual memory trace (Squire, 2006) (1.4). Figs. 2 and 4 and Tables 1 and 2 show that even when the reminder is expected to strengthen

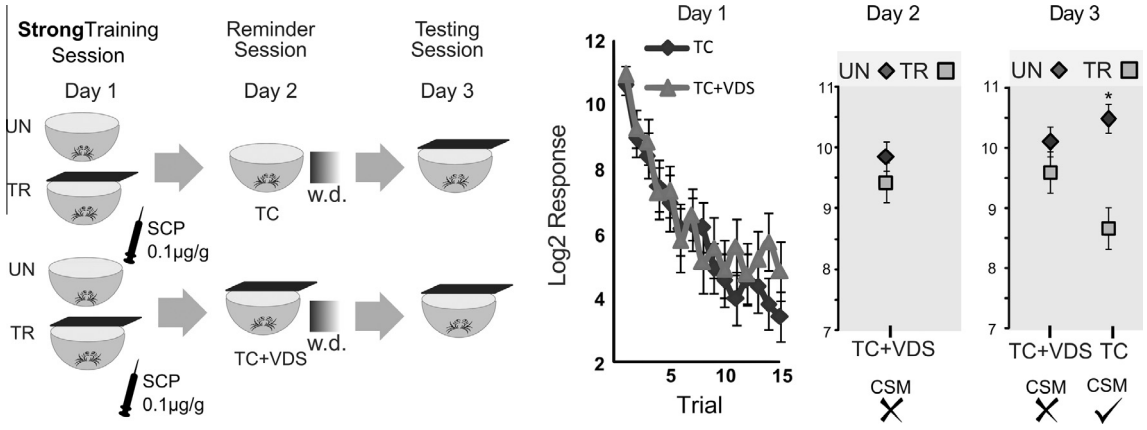

Fig. 4. Recovery of memory expression after the amnesic effect of scopolamine: memory is accessed and used even when the trace is not behaviorally expressed. Immediately after Training, all animals were injected with scopolamine (SCP) (0.1 µg/g). On Day 2, *Reminder Session* (see Fig. 2). Testing Session (Day 3): memory expression was disclosed for animals of TC groups, but not when animals were exposed to the reminder without the VDS. Symbols as in previous figures (adapted from Caffaro et al. (2012)).

Table 2
Select results showing that scopolamine treatments interfere with memory expression without disrupting LTM persistence. *Symbols:* water deprivation (w.d.) and scopolamine 0.1 µg/g (SCP). SCP → STP refers to SCP pre-training administration. SCP (5 µg/g): experiments performed with 5 µg/g. (+) Denotes long-term memory expression; (−) denotes no long-term memory expression. [1] (Beron de Astrada and Maldonado, 1999); [2] (Caffaro et al., 2012).

Training		Treatment on			
		Consolidation		Reconsolidation [2]	
	CSM		CSM		CSM
Strong Training Protocol (STP)	+				
		SCP [1]	–		
		SCP [1]	–	remind.sess. plus w.d.	+
		SCP [1]	–	novel context plus w.d.	–
		SCP [1]	–	remind.sess. plus VDS and w.d.	–
SCP → STP	–				
SCP → STP	–			remind.sess. plus w.d.	+
SCP → STP	–			novel context plus w.d.	–
SCP → STP	–			remind.sess. plus VDS and w.d.	–
STP		SCP (5 µg/g) [2]		remind.sess. plus w.d.	–
SCP → STP (5 µg/g)				remind.sess. plus w.d.	–

the memory (because more cues, i.e. the VDS, are being presented), the process of CSM reconsolidation is not initiated (no new information seems to be available, i.e. there is no mismatch). Recovery of memory expression after the reminder is only observable when activation occurs under the parametric conditions that trigger reconsolidation. It does not seem plausible to explain this case as an addition or summation of sub-threshold memory traces, non-associative memories formed during both sessions, or other putative associative memories not related to the VDS-context association formed during training (Gold, 2006; Hardt et al., 2009; Squire, 2006). As previously mentioned for the amnesic effect of the angiotensin II antagonist, scopolamine-treated animals do build a consolidated (and comparable to the unexpressed long-term memory generated by weak training protocols (Frenkel et al., 2010b)). The neural representation of a VDS-context association persists after the scopolamine administration; this representation can be activated by a reminder, then the mismatch conditions are evaluated, and can enter a new labile phase.

The other traditional alternative explanation of experimental amnesias is the retrieval block hypothesis (1.4): amnesia occurs when a memory is "stored" but is rendered inaccessible by the amnesic treatment (Gold and King, 1974; Hardt et al., 2009; Miller and Matzel, 2006; Nader and Wang, 2006). During consolidation, retrieval links are built up and the amnesic agent may damage those links or induce incomplete consolidation due to weak training. These dysfunctional retrieval links, however, can become functional under certain circumstances (noncontingent treatments, reminder, etc.). Nonetheless, the main point of our studies using angiotensin II and muscarinic antagonists (and weak trainings) is not that this experimental amnesia is reversed, but that such reversion depends on reconsolidation. The hypothesis can also be adjusted to others models that, for instance, explain transient amnesia following disruptions of memory consolidation and reconsolidation with models that circumvents the "storage versus retrieval" debate by viewing memory loss and recovery within the framework of distributed traces that can change over time and endogenous reinforcement (Amaral et al., 2008). Recoveries can be envisioned as "memory expression recoveries." LTM maintains, although unexpressed, the probability of being accessed and activated, enter the labile phase allowing a change in the hierarchy of the memories that can potentially control behavior.

The discussion presented before is actually valid not only for the scopolamine results, but for weak training as well. The consolidated memory trace does not take control of behavior in the long term because of (a) administration of the amnesic agents scopolamine or saralasin before or after strong training or (b) the weak training session. However, the experience-dependent internal representation (CSM) is accessed and activated by the reminder, the predicted and the reminder condition compared and, if a mismatch is found, LTM may enter the labile phase. In other words, memory is accessed and used even when the trace is not behaviorally expressed (Fig. 3).

In our design, what is evaluated at testing is not whether a memory survives or not, but whether it has been previously activated and become labile by the presentation of a reminder under conditions that trigger the reconsolidation process. Therefore, the approach shown here provides the retrieval and storage views of amnesias with a new prediction in the event of amnesia being reversed specifically upon reconsolidation. On the occasion of negative results, as with cycloheximide (Frenkel et al., 2010b), NMDA antagonists (F. Maza, A. Delorenzi, personal communication) or a very high dose of scopolamine (5 μg/g) (Table 1) (Caffaro et al., 2012), it is not possible to dissect whether the interference affected the consolidation process or, alternatively, obstructed the formation of the necessary links for the retrieval process (Miller and Matzel, 2006).

3.2. Rodent fear memory

This approach was successfully applied to test the hypothesis regarding the amnesic effects of scopolamine in the rodent fear memory. Choline reverses scopolamine-induced memory impairment by modulating memory reconsolidation and this memory impairment can be explained as a memory expression failure (Blake et al., 2012). Furthermore, the hypothesis is consistent with recent experimental findings in rats using the contextual fear paradigm. Rats subjected to a weak training procedure (a single exposure to a context-mild footshock experience) exhibited similar levels of freezing during testing to those that did not experience the association of shock and context. However, if rats are (a) previously exposed to an environmental challenge and later subjected to the weak training procedure or (b) trained and later (24 h) stressed prior to memory activation (48 h after training) by reminders, they show evident LTM, despite the weak training session. Outstandingly, this promoting influence on memory is not only evident during retrieval 24 h after training but also noticeable several days after in a subsequent test (Giachero et al., 2013; Maldonado et al., 2014, 2011). In light of the present hypothesis, these findings indicate that the memory trace generated by weak training remains behaviorally unexpressed. The memory trace does not take control of the fear behavior and only becomes evident in the long-term if the emotional stimulation is performed a day before memory activation by a reminder, or a day before learning. Therefore, under such conditions these memories without expression can be reactivated and enhanced. Obviously, these studies did not show that the mismatch condition at reminder is necessary to trigger the stress-promoting influence in the long term. Further experiments are necessary to find the mismatch and no-mismatch conditions at reminder sessions in this memory paradigm.

4. Memory labilization/reconsolidation is independent of memory expression

The studies presented before were part of few suggesting that there should be a dissociation between the mechanisms mediating memory activation (i.e. access to the memory trace) and those underlying the behavioral expression of memory (Sevenster et al., 2012). In line with this idea, recent studies have shown that the blockade of glutamate receptors actually disrupts retrieval but that this disruption has no consequence in the amnesic properties of protein synthesis inhibitors after memory reactivation (Ben Mamou et al., 2006; Milton et al., 2013). Is it possible to disrupt retrieval independent of memory activation or expression?

Research on memory consolidation (and now reconsolidation) has been fruitful, leading to a well-developed current knowledge of the mechanisms involved in memory formation. The same cannot be said of memory retrieval. While theoretical conceptions about memory retrieval exist, research examining these theoretical conceptions – for instance, via pharmacological induction of retrieval deficits (Barros et al., 2003; Si et al., 2004; Summers et al., 2003) – has been limited (Dudai, 2002a; Summers et al., 2003). The question of whether memory expression is required for LTM to become labile again is a crucial issue in the intersection between theoretical concepts and empirical data on the retrieval process. Taking into account that reconsolidation theory states that memory activation is necessary to induce the post-reminder state of malleability (Dudai, 2012; Lewis, 1979; Pedreira and Romano, 2013), we tested whether memory reactivation and memory expression can be affected independently by glutamate antagonists administered before memory reactivation in crabs.

The administration of glutamate receptor antagonists is typically used to interfere with memory during reconsolidation, an amnesic effect showed in several paradigms across phyla, *Neohelice* included (Pedreira et al., 2002; Lee et al., 2006; Rose and Rankin, 2006; Sara and Hars, 2006; Nikitin and Solntseva, 2012; Izquierdo et al., 2004; Si et al., 2004; Milton et al., 2013). Additionally, recent studies have shown that AMPA receptor blockade actually disrupts retrieval without affecting the amnesic properties of protein synthesis inhibitors after memory reactivation (Ben Mamou et al., 2006; Rodriguez-Ortiz et al., 2012). Moreover, the use of NMDA or AMPA antagonists to investigate the role of glutamate neurotransmission in the retrieval process has also been widely studied (Barros et al., 2003; Si et al., 2004; Summers et al., 2003). Therefore, our working hypothesis was that NMDA or AMPA antagonists can induce a retrieval deficit that is due to a disruption of memory expression, but the potential for memory to be reactivated, accessed, used (for mismatch evaluation) and become labile remains unaffected.

Fig. 5 shows that, although the NMDA receptors antagonist APV deeply attenuates memory expression to undetectable levels, the antagonist has long-term amnesic effects when applied specifically during a reminder session that triggers reconsolidation (Barreiro et al., 2013). The result of this study illustrates that even in the absence of expression, memory can be reactivated, the mismatch can be evaluated, and later the memory labilized. Traditional controls regarding reconsolidation-effects (Nader et al., 2000), including the necessity for the reminder, the temporal window after memory activation and that the amnesic effect needs time to develop, were tested (Barreiro et al., 2013). Critical controls of this study regarding the mismatch condition at the reminder session show that the amnesic effect of the NMDA antagonist APV depends on memory activation–labilization of the non-expressed memory. Memory can be interfered with by the administration of APV during reconsolidation, regardless of whether the expression of the memory is attenuated before the reminder is presented. Remarkably, the amnesic effect does not occur when reinforcement is presented during the reminder because there is no mismatch for the reminder (Figs. 5 and 6). This study, focused on retrieval interference (Barreiro et al., 2013), also supports the notion that memory activation–labilization and expression can be dissociated. Certainly, a dissociation for the requirement of different NMDA receptors for memory destabilization and restabilization has been shown (Milton et al., 2013). However, our study specifically avoids other post-retrieval consequences that are independent of the reconsolidation process (Cahill et al., 2001; Gisquet-Verrier and Riccio, 2012). Memory activation *per se* is not sufficient to achieve

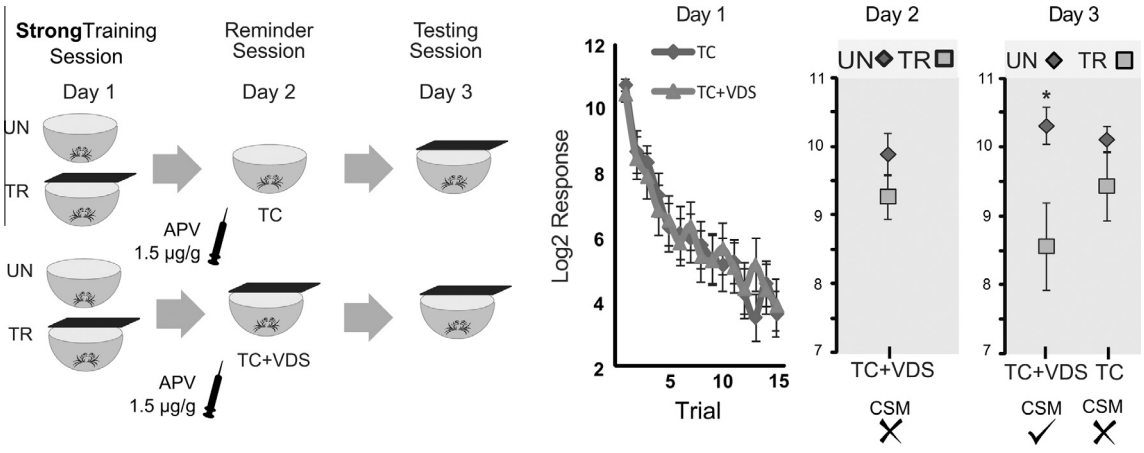

Fig. 5. Memory activation is independent of memory expression. Day 1, Training Session. Day 2, all animals were injected with APV (1.5 µg/g). *Reminder Session*, see Fig. 2. Day 3 (Testing Session), memory was tested with a single VDS presentation. Symbols as in previous figures. Adapted from Barreiro et al. (2013).

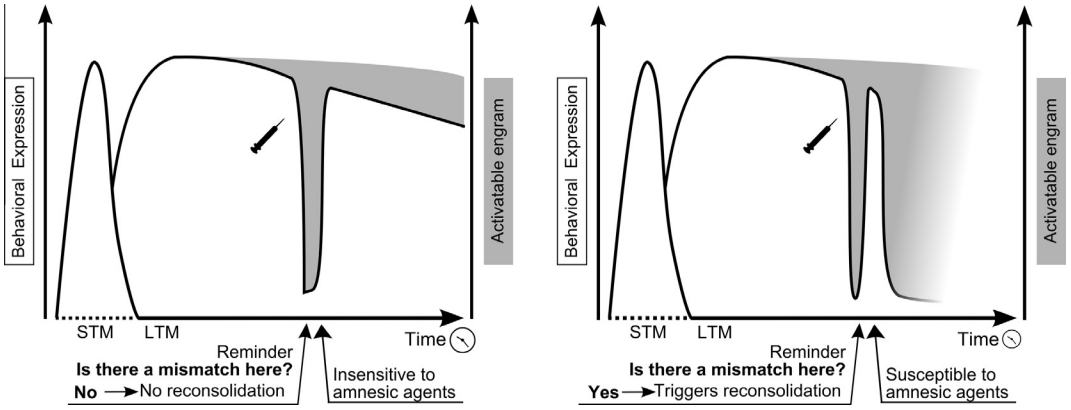

Fig. 6. Memory can be interfered with amnesic agents during reconsolidation, independently of its behavioral expression. Behavioral expression and the activatable persistent engram of a memory are represented as in Fig. 3. Here, although memory expression is deeply attenuated (e.g. by administration of NMDA antagonists), memory activation occurs and memory is interfered with by the amnesic agent action during reconsolidation. Left, reminder condition that does not trigger reconsolidation, memory expression is just attenuated during the effects of APV administration. Right, as the reminder presents mismatch conditions, reconsolidation is triggered and the amnesic effects of amnesic agents are disclosed in the long, but not the short, term.

the amnesic actions of the NMDA antagonist APV. Unlike recent studies (Milton et al., 2013; Rodriguez-Ortiz et al., 2012), the experimental approach allowed us to discern that pre-reminder APV administration does not interfere with either the potentiality of the memory to be activated or with the appraisal of mismatch conditions; rather it affects the behavioral expression of the memory trace (Barreiro et al., 2013) (Fig. 6). In this line, a recent and remarkable study shows that the "destabilization–reconsolidation" of a contextual fear memory is dependent upon hippocampal neuronal activity, but not memory expression (Lee and Flavell, 2014).

It should be noted that APV results discussed here appear to be dissimilar with the results of Ben Mamou et al. (2006): the dose of APV used did not prevent memory expression or reconsolidation when infused in amygdala prior to retrieval, but protected memory from anisomycin-induced impairments. Several studies report that retrieval requires intact glutamate receptors in several brain areas, but AMPA and NMDA receptor antagonist can affect the process depending on the route of administration (Ben Mamou et al., 2006; Izquierdo et al., 2004; Milton et al., 2013; Rodriguez-Ortiz et al., 2012). Different memory models, doses and routes of administration appear to be the main source of difference between these studies (discussed in Barreiro et al. (2013)).

5. Forgetting a declarative memory: a loss in memory expression of activatable memories?

The above mentioned studies strongly suggest that the mechanisms mediating memory activation and the mechanisms that underlie the behavioral expression of memory can be dissociated, offering a new scenario for the understanding of human memory persistence. Although reconsolidation has also been attained in humans, including verbal memory (Forcato et al., 2007, 2010), memory of a motor skill task (Walker et al., 2003), episodic memory (Hupbach et al., 2007), autobiographic (Schwabe and Wolf, 2009, 2010) and fear conditioning (Kindt et al., 2009; Schiller et al., 2010; Soeter and Kindt, 2010), memory enhancing effects during this process had not been reported in humans at that time (Agren, 2014; Bos et al., 2014; Dudai, 2012; Forcato et al., 2011; Pedreira, 2013; Rodriguez et al., 2012; Schwabe et al., 2014; Stern and Alberini, 2013).

Aiming to evaluate whether the expression of a previously consolidated memory could be enhanced during reconsolidation in humans, we used a paradigm of pairs of cue–response syllables where the reminder structure that triggers reconsolidation was established. The laboratory under the supervision of Dr Maldonado developed this paradigm based on Müller and Pilzecker's original study (Dewar et al., 2007), in which the mismatch condition (1.3) of a human memory was described for the first time (Forcato et al., 2009, 2007, 2010; Rodriguez et al., 2012).

5.1. The human declarative memory paradigm

The above memory paradigm has been recently reviewed (Pedreira, 2013). Briefly, volunteers learn an association between five cue-syllables and their respective response-syllables. Similar to the experiments described above, each three-session experiment consists of training, reminder and testing sessions (Fig. 7). Participants have to learn a list of five pairs of nonsense syllables (five pairs of nonsense cue–response-syllables in Spanish: for instance, ITE-OBN (bold type: cue-syllable; regular type: response-syllable)). Each training trial is comprised of a context period, where a light-image-sound combination is presented during the syllable presentation to predict the list apparition. First, the list appears on the computer screen and the subject tries to memorize each response syllable associated with the matched cue syllable. In the following trials, cue-syllables from the list are presented and an empty response-box appears where the subjects are given 5 s to write down the corresponding response-syllable. If no response syllable is written down, the correct syllable is shown for 4 s; if an incorrect response syllable is written down, it is replaced by the correct syllable in red and it is shown for 4 s; if the correct response is given, it stays for 4 s longer. Immediately after any of these three situations, another cue-syllable is shown and the process is repeated again in semi-random order until the list is over.

5.2. Reconsolidation of a human declarative memory and the mismatch component needed to trigger it

As for non-human animals, there should be a mismatch during the reminder to labilize the consolidated memory. In this declarative memory paradigm, such a mismatch is induced by forcing the subject to stop the session before he can respond to the first syllable associated with the cue syllable during the reminder session. This session (day 6 or 20 in our studies) begins the same as the training session, with the context and immediately after its presentation – as expected – a cue-syllable appears on the left-hand side of the monitor screen together with the response-box (details in Coccoz et al. (2011) and Forcato et al. (2009)). However, 2 s later, a notice displayed on the monitor announces that the session has to be suspended, thus not allowing the subject to write down the response-syllable in the response-box. As a control, a reminder that does not labilize and hence does not trigger reconsolidation is used (Forcato et al., 2010). This reminder starts the same way, with the context followed immediately by one cue-syllable, but now subjects are allowed to write down the response-syllable in the response-box for a period of 5 s, and later a notice displayed on the monitor announces that the session has to be suspended. This reminder does not initiate the process of reconsolidation.

Immediately after the reminder session, subjects are led to an adjacent room and receive the respective treatment. The testing session consists of a memory evaluation of the 5 cue-response syllables acquired during training, but in random order (one trial) (Coccoz et al., 2011, 2013).

5.3. Enhancing declarative memory during reconsolidation

Our working hypothesis was that during memory reconsolidation, neuromodulators can determine the ability of the memory to guide behavior by increasing its conscious access (Coccoz et al., 2011). In light of this, after forgetting, a memory trace is not consciously accessed but could be activated and labilized by the appropriate reminder (the term forgetting is applied here to items that were once retrievable from LTM but no longer are, despite using the same retrieval cue in both cases (Wixted, 2007)). Consequently, we predicted that we might be able to improve the behavioral expression or conscious access to a forgotten LTM if a memory modulator was given concomitantly with reconsolidation. We used positive modulation of memory expression during reconsolidation to determine whether one or three-week-old forgotten memories could be behaviorally re-expressed by one of two different real-life events known to enhance memory presented during memory reconsolidation: a mild stressor and glucose.

Why a stressor? Stressors and stress hormones are powerful modulators of memory processes (Cahill and van Stegeren, 2003; McGaugh, 2000, 2006; McGaugh and Roozendaal, 2002; Sandi and Pinelo-Nava, 2007; Wolf, 2009). With the aim of evaluating whether this declarative memory can be modulated by concurrent experiences during reconsolidation, we used the cold pressor stress

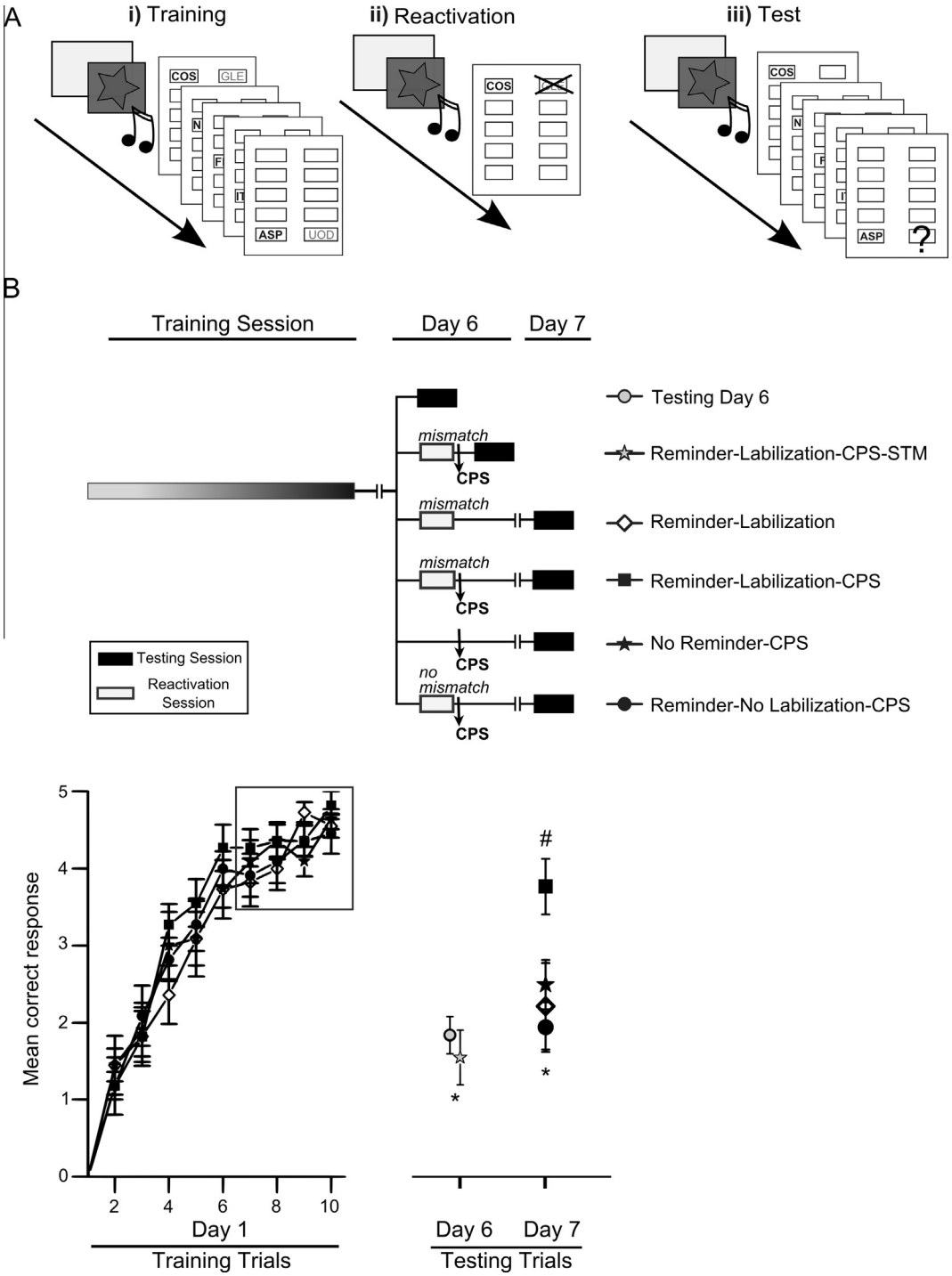

Fig. 7. Enhancing declarative memory during reconsolidation: the memory effects of Cold Pressor Stress (CPS) administration during reconsolidation. A. (i) *Training Session:* includes 10 trials with the correct context followed by the list, mixed with fake contexts. Subjects are given 5 s to write down the corresponding response-syllable. Each List is composed of five constant pairs of nonsense cue–response-syllables that appear on the screen pseudo randomly. (ii) *Reactivation Session:* shown, the reminder structure that triggers labilization–reconsolidation, in which the correct context is followed by the presentation of one cue-syllable without allowing the subject to respond with the respective response-syllable. The Reminder-No Labilization: reminder structure that does not trigger reconsolidation comprised the specific context, but subjects are allowed to write down the first response-syllable (5.2). (iii) *Testing Session:* one trial of the whole list learned on Day 1. B. During the Training Session (Day 1) all groups received 10 trials, the last four of which are shown in the box (tail of training). Unlike testing on Day 3 (data not shown), poor memory performance was found at testing on Day 6. For the Reminder-Labilization-CPS-STM group, no enhancement of memory performance was disclosed in the short term (STM) after CPS. Memory enhancement 24 h later (Day 7) was only disclosed for the Reminder-labilization-CPS group, in which memory was modulated by CPS during a reconsolidation process triggered by the mismatch condition of the reminder on Day 6. Mean correct responses ± SEM are shown. (*) Significant differences at testing compared to the training tail, (#) significant differences at testing compared to the three control groups on Day 7, described in the respective study (adapted from Coccoz et al. (2011)).

(CPS). CPS is a treatment widely used in neuroscience research that indeed enhances memory consolidation in humans (Anderson et al., 2006; Cahill and van Stegeren, 2003; Luethi et al., 2008; McGaugh, 2006; McGaugh and Roozendaal, 2009; Nielson and Bryant, 2005; Nielson and Lorber, 2009; Nielson and Powless, 2007; Smeets et al., 2008; Wolf, 2009); (but see (Schwabe and

Wolf, 2010; Wichert et al., 2011). Why glucose? Like stress hormones, the administration of glucose during consolidation has also been largely employed as an enhancing agent of cognitive functions in humans and non-human animals (Gold, 1986, 2008a; Kopf et al., 1993; Manning et al., 1993; Messier, 2004; Oomura et al., 1993). In fact, glucose improves verbal memory in both healthy young adult and aged populations (Gold, 2005; Manning et al., 1993; McNay and Gold, 2002; Messier, 2004; Newman et al., 2011).

We expected that after forgetting there would be a memory trace that would not be consciously accessed using free recall but could be reactivated and labilized by the appropriate reminder. Fig. 7B shows a compilation of results of the study (Coccoz et al., 2011). In contrast to the memory tested 3 days after training (Forcato et al., 2007), a poor memory performance was found after 6 days' delay. However, when the CPS administration was concurrent with the activated and labile memory, a robust memory expression was obtained the day after the reminder was presented. The enhanced memory expression at testing was revealed only when CPS was contingent upon reconsolidation 24 h post training and not when tested short term, showing that the improving effect was reconsolidation-specific because it needed time to develop (Alberini, 2007; Baratti et al., 2009; Dudai, 2006; Frenkel et al., 2005b; Pedreira et al., 2004; Rodriguez et al., 2012; Schiller et al., 2010). Warm water administration during reconsolidation, even after using the reminder that could labilize the memory, was unable to alter memory expression. The performance also remained low at testing when memory was not activated. Remarkably, only when the CPS was given after the reminder that triggers the memory expression was the effect noticed (Fig. 7B) (Coccoz et al., 2011).

Our next study showed that the naturalistic mild stressor can enhance memory during reconsolidation 6 but not 20 days after training, when the forgetting effect was greater and very poor memory expression was detected (Coccoz et al., 2013). The very low memory performance found in the cue-recall test three weeks after training was due to forgetting, resulting from a lack of expression and not from a persistence deficit: we showed that subjects exhibited high memory expression when asked to recognize the syllables from a list (Coccoz et al., 2013) as expected in retrieving memories through recall and perceptual recognition (Craik, 2007; Eichenbaum, 2007; Tulving and Schacter, 1990). We hypothesized that the very poor performance obtained through cue-recall of this three-week-old memory might reflect a lack of conscious access, while the potential of the memory to be activated and labilized by the presentation of a reminder lasted. Indeed, the memory persisted and could be activated and enhanced even 3 weeks after training, when syllables were almost completely forgotten. Unlike CPS, results showed that the oral administration of a glucose-rich juice – but not a diet juice – after the reminder that triggers reconsolidation was able to enhance LTM expression (Fig. 8) (Coccoz et al., 2013), proving that this declarative memory can in fact be activated, become labile and improved even if it is not consciously accessed three weeks after training.

It is important to note that the memory enhancement during reconsolidation in non-human and human memory models

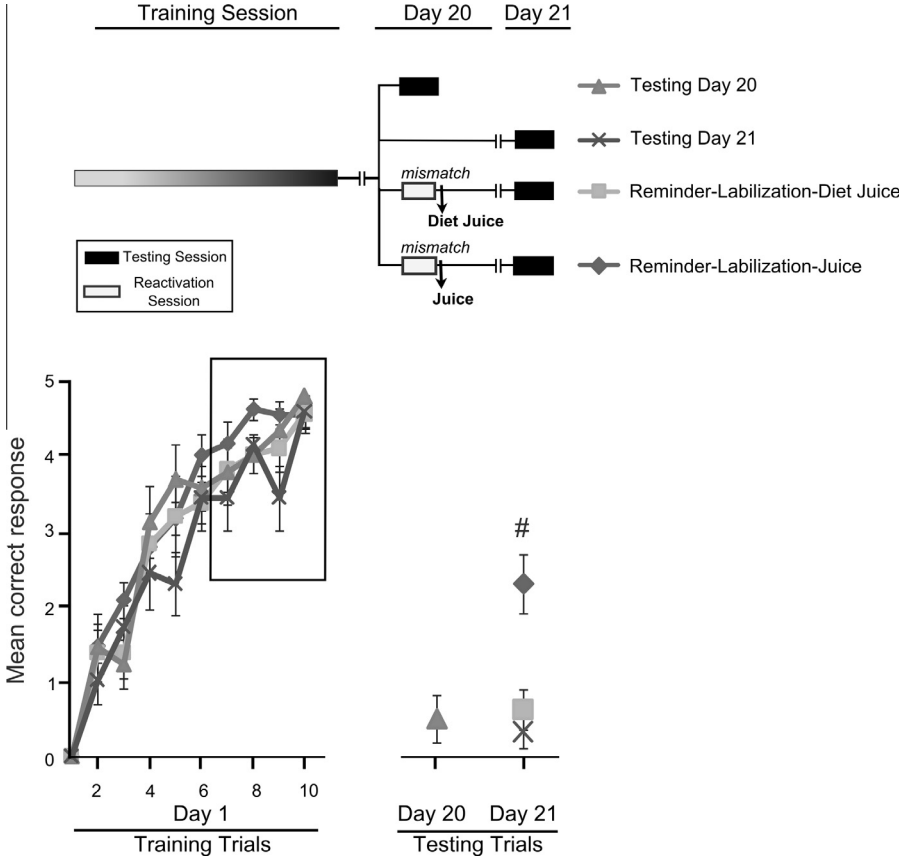

Fig. 8. Glucose administration during reconsolidation enhances forgotten memory. Experimental sessions as described in Fig. 7A. *Experimental design:* the Reminder-Juice-21d group included the reminder structure that triggers labilization–reconsolidation followed by drinking the glucose juice on Day 20. The testing session was performed 24 h after reactivation. The Reminder-Diet Juice-21d group had the same structure as the previous one, but diet juice replaced glucose juice. The 20d-Testing and the 21d-Testing groups had the Testing Session without a prior Reactivation Session. During the Training Session (Day 1) all groups received 10 trials, the last four of which are shown in the box (tail of training). During the Testing Session (Day 21) only the Reminder-Diet Juice-21d group made significantly more correct responses compared to Reminder-Diet Juice-21d, the 20d-Testing and 21d-Testing groups. (#) Significant differences at testing compared to control groups at testing, described in the respective study (adapted from Coccoz et al. (2013)).

reported by others (Rodriguez et al., 1999; Soeter and Kindt, 2012; Stern and Alberini, 2013; Tronson and Taylor, 2007) was revealed as an increase in the expression of a certain response, e.g. an increase in freezing levels or a decrease in escape responses (but see Bos et al. (2014)). In the studies regarding declarative memory revised here, all control groups showed the expected low or very low memory expression one or three weeks after training due to the natural process of forgetting (Wixted, 2007). The specific information of the nonsense cue–response-syllables must have persisted to be activated – the mismatch conditions evaluated – become labile and then expressed at long-term if the CPS or glucose administration was contingent upon reconsolidation. Therefore, the probability of the cue–response syllable memory being consciously accessed at the testing session may be modulated by naturalistic events such as CPS or glucose during reconsolidation. In conclusion, our studies in humans support the view that conscious access is not required for a consolidated memory to be activated and then become labile by specific reminders.

6. Expression: one of the possible fates of activated memories

The studies reviewed in this article on the modulation of memory expression are concordant with our hypothesis, contrasting in some degree with canonical views (McGaugh, 2000). During memory consolidation and reconsolidation, neuromodulators can determine the probability of memory to guide behavior by either increasing or decreasing its behavioral expressibility, without affecting the potential of persistent memories to be activated and become labile (Caffaro et al., 2012; Coccoz et al., 2011, 2013; Frenkel et al., 2005a, 2010b; Smal et al., 2011). Moreover, results summarized here strongly support the notion that the mechanisms mediating memory activation and labilization, and the mechanisms that underlie the behavioral expression of memory can be dissociated; yet another element of memory processes that appears to be conserved throughout evolution (Barreiro et al., 2013; Ben Mamou et al., 2006; Caffaro et al., 2012; Coccoz et al., 2013; Finn et al., 2012; Frenkel et al., 2011, 2005a, 2010b; Lee and Flavell, 2014; Menzel, 2012; Rodriguez-Ortiz et al., 2012; Sevenster et al., 2012).

Considering the studies discussed here, the traditional view of the "strength" of a particular memory trace would refer to the probability of the trace taking control of behavior during testing. The potential of a persistent memory to be activated and become labile by specific reminders remains unaffected even if, for instance, the memory is not consciously accessed in human declarative memories (Coccoz et al., 2011, 2013) or memory expression is not disclosed both in crabs and in rodents (Blake et al., 2012; Caffaro et al., 2012; Frenkel et al., 2005a, 2010b; Maldonado et al., 2014). This fact is consistent with the seminal notions that propose that LTMs should first be activated, and then a subsequent process will determine whether they can or cannot be behaviorally expressed (Tulving, 1983). The enhancement of reconsolidation that improves the behavioral expression of LTM might be due to changes in decision-making processes that intervene between the activated memory and the behavioral response (Shadlen and Kiani, 2013). In this view, the reinforcement or modulation of processes that are critical for long-term memory expression (Dudai and Eisenberg, 2004) is part of the general organization of brain function which incorporates flexible decision-making on the basis of complex computations negotiating internal and external processing (Brembs, 2011; Menzel, 2012). Consequently, it is possible that reconsolidation reflects a process that allows memory re-evaluation, changing the hierarchy of the memories that can potentially control behavior. Memory expressibility – the outcome of experience-dependent changes in 'the potential to behave' (Dudai, 2007) – may be considered a flexible and modulable attribute of long-term memories.

Accordingly, the amnesic effects found in human fear memories during reconsolidation would target the mechanisms that underlie the behavioral expression of the emotional components of fear memory, but not necessarily affect the memory *per se*, i.e. memory persistence (Kindt et al., 2009; Sevenster et al., 2012, 2013; Soeter and Kindt, 2010). Therefore, although the absence of memory expression is largely insufficient to imply that unexpressed memory traces are lost, for instance after experimental amnesias or forgetting (Amaral et al., 2008; Cahill et al., 2001; Eichenbaum, 2007; Gold, 2006; Gold et al., 1973; Lewis, 1976; Philips et al., 2006; Rovee-Collier et al., 1980), our reconsolidation studies support the hypothesis that memory expression is not a requirement for LTMs to be activated and become labile. Expression is not necessary to either activate LTMs or to use the information learned to evaluate mismatch conditions (Barreiro et al., 2013; Ben Mamou et al., 2006; Blake et al., 2012; Caffaro et al., 2012; Coccoz et al., 2011, 2013; Dudai, 2012; Frenkel et al., 2005a, 2010b; Rodriguez-Ortiz et al., 2012).

Fig. 9 outlines our proposal: when the same reminder cues are used, the periods in which a memory – which was once expressed – can be activated and become labile exceed the periods in which the memory can be expressed or consciously accessed. Actually, we propose that this view would add new features to the concepts of

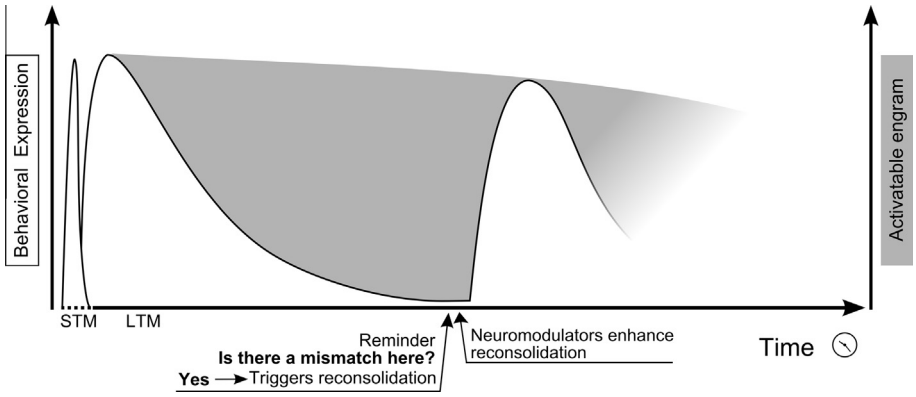

Fig. 9. Proposed model for the dynamics of behavioral expression and the activatable engram of memory. Behavioral expression (white) and the activatable persistent engram (gray) of a memory are represented. In this view, memories can be activated and labilized even after being forgotten. The scheme describes the decay of memory performance of a consolidated memory due to the natural process of forgetting (LTM-behavioral expression: the expression of a representation in cognition or behavior). However, despite being unexpressed, memory persists, can be accessed and activated by the reminder, and, if a mismatch is found, it may enter the labile phase (LTM-activatable engram: LTM defined as the retention over time of the experience internal representations, or the potential to reactivate such representations (Dudai, 2002a)). If reconsolidation is enhanced, behavioral expression can be recovered.

memory persistence and forgetting (Eichenbaum, 2007; Katche et al., 2013; Tulving and Schacter, 1990; Wixted, 2004, 2007).

In brief, the hypothesis discussed here proposes that memory expressibility is a flexible, modulable attribute of long-term memories that enables continuous adaptation of behavior to changing environmental and bodily constraints. Retrieval and memory expression are therefore not interchangeable concepts; the terms: active, labile and expression will be useful for more exhaustive descriptions of the processes triggered by reminders (Barreiro et al., 2013; Lee and Flavell, 2014; Lewis, 1979). Adding the decision-making perspective to memory activation and expression perhaps can help (Shadlen and Kiani, 2013).

Conceivably, our studies may provide relevant insights into the nature of memory and memory enhancement during reconsolidation, in both humans and non-human animals, where unexpressed memories can be activated and positively modulated by concurrent experiences. This issue might have significant implications for the understanding of memory persistence in humans and non-human animals (Bekinschtein et al., 2008; Eichenbaum, 2007; Henke, 2010; Tulving and Schacter, 1990), for the comprehension of the basis of some mnesic disorders and for the design of novel strategies to enhance memory in health and in pathological conditions (Alberini and Chen, 2012; Dudai and Morris, 2013; Toomey and Ecker, 2009).

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