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Retrieval under stress decreases the long-term expression of a human declarative memory via reconsolidation

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ABSTRACT

Acute stress impairs memory retrieval of several types of memories. An increase in glucocorticoids, several minutes after stressful events, is described as essential to the impairing retrieval-effects of stressors. Moreover, memory retrieval under stress can have long-term consequences. Through what process does the reactivated memory under stress, despite the disrupting retrieval effects, modify long-term memories? The reconsolidation hypothesis proposes that a previously consolidated memory reactivated by a reminder enters a vulnerability phase (labilization) during which it is transiently sensitive to modulation, followed by a re-stabilization phase. However, previous studies show that the expression of memories during reminder sessions is not a condition to trigger the reconsolidation process since unexpressed memories can be reactivated and labilized. Here we evaluate whether it is possible to reactivate-labilize a memory under the impairing-effects of a mild stressor. We used a paradigm of human declarative memory whose reminder structure allows us to differentiate between a reactivated-labile memory state and a reactivated but non-labile state. Subjects memorized a list of five cue-syllables associated with their respective response-syllables. Seventy-two hours later, results showed that the retrieval of the paired-associate memory was impaired when tested 20 min after a mild stressor (cold pressor stress (CPS)) administration, coincident with cortisol levels increase. Then, we investigated the long-term effects of CPS administration prior to the reminder session. Under conditions where the reminder initiates the reconsolidation process, CPS impaired the long-term memory expression tested 24 h later. In contrast, CPS did not show effects when administered before a reminder session that does not trigger reconsolidation. Results showed that memory reactivation-labilization occurs even when retrieval was impaired. Memory reactivation under stress could hinder -via reconsolidation- the probability of the traces to be expressed in the long term.

1. Introduction

There is growing consensus that a single stressful experience modulates memory processes (Roozendaal, McEwen, & Chattarji, 2009; Sandi & Pinelo-Nava, 2007; Wolf, 2009). In fact, both human and non-human studies show that emotionally relevant events activate hormonal and brain systems that enhance the consolidation of newly acquired memories (McGaugh & Roozendaal, 2002). Thus, endogenous modulating systems provide a basis for selecting experiences for long-term storage (McGaugh, 2000). In contrast to such promoting influence during consolidation, acute stress impairs memory retrieval (Gagnon & Wagner, 2016; Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003). Thus, stress experience before testing impairs the retrieval of several types of memories including declarative and episodic (Roozendaal, 2002; Roozendaal & McGaugh, 2011); but see (Schwabe & Wolf, 2014). The release of glucocorticoids shortly after stress is described as a key factor of such impairing influence (Roozendaal & McGaugh, 2011). While the impairing effect on retrieval is stronger for

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emotionally arousing items, this effect has been also documented for neutral information (Gagnon & Wagner, 2016; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009; Wolf, Kuhlmann, Buss, Hellhammer, & Kirschbaum, 2004).

Views regarding retrieval are shifting under the light of reconsolidation findings (Dudai & Morris, 2013; Miller & Matzel, 2006; Nader & Wang, 2006; Sara & Hars, 2006). Our previous studies highlighted that retrieval and memory expression are not interchangeable concepts. Hence, memory expression during the reminder session is not a prerequisite to trigger reconsolidation since unexpressed memories can be reactivated and reconsolidated (Barreiro, Suarez, Lynch, Molina, & Delorenzi, 2013; Blake, Boccia, Krawczyk, Delorenzi, & Baratti, 2012; Caffaro, Suarez, Blake, & Delorenzi, 2012; Coccoz, Maldonado, & Delorenzi, 2011; Frenkel, Maldonado, & Delorenzi, 2005; Frenkel, Suarez, Maldonado, & Delorenzi, 2010; Maza, Locatelli, & Delorenzi, 2016). For instance, we showed in crabs that the retrieval deficit induced by a pharmacological manipulation (administration of glutamate receptor antagonists) interferes with memory expression (Barreiro et al., 2013; Delorenzi et al., 2014). However, the memory trace retains the potentiality of being reactivated. Indeed, the information can be accessed and used for mismatch evaluation (disparities between the retrieval conditions and the reactivated representation of the experience); the occurrence of reconsolidation depends on detecting mismatches between actual and expected experiences during the reminder session (Pedreira & Romano, 2013). Surprise, i.e. a rupture of the expectations generated by a mismatch between the retrieval conditions and the reactivated representation of the experience (Barto, Mirolli, & Baldassarre, 2013; Rescorla & Wagner, 1972), is an essential boundary condition to initiate the reconsolidation process in several species (Diaz-Mataix, Ruiz Martinez, Schafe, LeDoux, & Doyere, 2013; Dudai, 2006, 2009; Fernandez, Boccia, & Pedreira, 2016; Forcato, Argibay, Pedreira, & Maldonado, 2009; Forcato et al., 2007; Frenkel et al., 2005; Lee & Flavell, 2014; Morris et al., 2006; Pedreira, Perez-Cuesta, & Maldonado, 2004; Pedreira & Romano, 2013; Sevenster, Beckers, & Kindt, 2012, 2013, 2014; Winters, Tucci, & DaCosta-Furtado, 2009). Our studies show that, although unexpressed, the memory trace becomes labile only when mismatch takes place during the reminder session (Barreiro et al., 2013; Caffaro et al., 2012; Delorenzi et al., 2014; Frenkel et al., 2005, 2010). These results suggest that there should be a dissociation between the neurobiological mechanisms mediating memory reactivation (i.e. the access to the memory trace (Lewis, 1979)) and those underlying the behavioral expression of memory (Delorenzi et al., 2014). Concordantly, other studies show this dissociation (Ben Mamou, Gamache, & Nader, 2006; Lee & Flavell, 2014; Milton et al., 2013; Rodriguez-Ortiz, Balderas, Garcia-Delatorre, & Bermudez-Rattoni, 2012; Santoyo-Zedillo, Rodriguez-Ortiz, Chavez-Marchetta, Bermudez-Rattoni, & Balderas, 2014).

We recently showed that the administration of a mild stressor (cold pressor stress (CPS)) or glucose ingestion, after memory reactivation, increase long-term expression of a human declarative memory. Remarkably, these memory improvements occur only when the reminder contains the mismatch conditions necessary to trigger reconsolidation (Coccoz, Sandoval, Stehberg, & Delorenzi, 2013; Coccoz et al., 2011; Delorenzi et al., 2014). Regardless of poor memory expression at the time of memory reactivation due to forgetting (1 or 3 weeks after training), robust memory expression can be found at testing sessions if stress (1st week) or glucose administration (3th week) are concurrent with the reconsolidation phase. Thus, the behavioral expression of consolidated memories is not required for memory reactivation and reconsolidation (Barreiro et al., 2013; Ben Mamou et al., 2006; Blake et al., 2012; Delorenzi et al., 2014; Frenkel et al., 2005; Milton et al., 2013; Rodriguez-Ortiz et al., 2012; Santoyo-Zedillo et al., 2014; Sevenster et al., 2012).

Several literature suggest that pharmacological or behavioral manipulations during reconsolidation might result in a memory interference, disturbances that affect the memory persistence itself or a failure in subsequent retrievals (Agren et al., 2012; Schiller et al., 2010; Schwabe & Wolf, 2009; Wichert, Wolf, & Schwabe, 2011). Why does reconsolidation open an opportunity for the interference of consolidated memories? What might be the adaptive function of reconsolidation? In our view, a key function of reconsolidation is to induce a change in memory expression by the influence of a concurrent experience (Delorenzi et al., 2014; Frenkel et al., 2005). Reconsolidation is yet another example that the dynamics of the memory processes are conserved throughout evolution (Barco, Bailey, & Kandel, 2006; Dudai & Morris, 2013; Glanzman, 2010; Menzel, 1999), a feature that can be founded in the hypothesis of a common origin of the high-order memory centers in bilateral animals (Maza et al., 2016; Tomer, Denes, Tessmar-Raible, & Arendt, 2010; Wolff & Strausfeld, 2016). Phylogenetically distant species show a vulnerability to pharmacologic interventions during reconsolidation, from protein synthesis inhibitors to neuromodulators' agonists or antagonists, and to behavioral interventions; (Chen et al., 2014; Eisenberg, Kobilo, Berman, & Dudai, 2003; Lukowiak, Fras, Smyth, Wong, & Hittel, 2007; Nader, Schafe, & Ledoux, 2000; Pedreira, 2013; Pedreira & Maldonado, 2003; Przybyslawski & Sara, 1997). Our hypothesis is that, during reconsolidation, endogenous neuromodulators can determine the ability of the memory to guide behavior by decreasing or increasing its behavioral expression, without disturbing both its persistence and its capacity to be reactivated (Caffaro et al., 2012; Delorenzi et al., 2014; Frenkel et al., 2005, 2010; Maza, Locatelli et al., 2016). 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 affect memory persistence (Agren, 2014; Kindt, Soeter, & Vervliet, 2009; Kindt & van Emmerik, 2016; Sevenster et al., 2012; Soeter & Kindt, 2010).

The working hypothesis of the present study is that, despite stress-induced retrieval deficit (by administration of CPS before testing), the potential for a memory trace to be reactivated, used for mismatch evaluation and become labile remains unchanged (Delorenzi et al., 2014). According to other studies, the reactivation of a declarative memory after an increase in cortisol levels, due to a stressful experience or systemic administration, leads to both retrieval deficits and long-term memory attenuation (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2008a, 2008b; Tollenaar et al., 2009). A recent study shows similar result when fear memories are reactivated after a stressful experience (Meir Drexler & Wolf, 2016), but see Drexler, Merz, Hamacher-Dang, Tegenthoff, and Wolf (2015).

Here, we propose that, despite the retrieval deficit induced by CPS administration, the reactivation of this memory under stress leads to an attenuation of long-term memory expression through reconsolidation.

2. Experimental procedures

2.1. Participants

A total of 64 (36 women and 28 men) healthy undergraduate and graduate students participated as volunteers for the present study. Individuals who met any of the following criteria were excluded from participating: non-native Spanish speaking; current alcohol or substance abuse; cardiac disorders; hypertension; diabetes or treatment with psychotropic medications. All participating healthy volunteers were free of medication except for