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Stress enhances reconsolidation of declarative memory

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Summary Retrieval of negative emotional memories is often accompanied by the experience of stress. Upon retrieval, a memory trace can temporarily return into a labile state, where it is vulnerable to change. An unresolved question is whether post-retrieval stress may affect the strength of declarative memory in humans by modulating the reconsolidation process. Here, we tested in two experiments whether post-reactivation stress may affect the strength of declarative memory in humans. In both experiments, participants were instructed to learn neutral, positive and negative words. Approximately 24 h later, participants received a reminder of the word list followed by exposure to the social evaluative cold pressor task (reactivation/stress group, $n_{exp1} = 20$; $n_{exp2} = 18$) or control task (reactivation/no-stress group, $n_{exp1} = 23$; $n_{exp2} = 18$). An additional control group was solely exposed to the stress task, without memory reactivation (no-reactivation/stress group, $n_{exp1} = 23$; $n_{exp2} = 21$). The next day, memory performance was tested using a free recall and a recognition task. In the first experiment we showed that participants in the reactivation/stress group recalled more words than participants in the reactivation/no-stress and no-reactivation/stress group, irrespective of valence of the word stimuli. Furthermore, participants in the reactivation/stress group made more false recognition errors. In the second experiment we replicated our observations on the free recall task for a new set of word stimuli, but we did not find any differences in false recognition. The current findings indicate that post-reactivation stress can improve declarative memory performance by modulating the process of reconsolidation. This finding contributes to our understanding why some memories are more persistent than others.

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1. Introduction

The malleable nature of human memory is crucial for adequate adaptation to an ever-changing environment. Given that a stimulus or context may not predict danger or reward forever, it is essential that our memories remain open to modification. One process that provides an opportunity for such modification is memory reconsolidation. Upon retrieval, a memory trace may return into a labile, protein-synthesis dependent state where it is susceptible to modifications (Nader, 2003). Mere retrieval is however not sufficient to induce memory reconsolidation (Pedreira et al., 2004; Forcato et al., 2009; Lee, 2009; Sevenster et al., 2013). The experience of a prediction error — i.e., the mismatch between the actual and expected experience based on prior learning — appeared to be a prerequisite to destabilize the previously formed memory trace (Pedreira et al., 2004; Sevenster et al., 2013). This destabilization enables the memory trace to be updated either by simply changing the strength of the original memory trace (e.g., Nader et al., 2000; Frenkel et al., 2005; Kindt et al., 2009; Soeter and Kindt, 2010, 2011, 2012) or by integrating new information into the memory trace (e.g., Forcato et al., 2007; Hupbach et al., 2007).

Memory reconsolidation is typically demonstrated through the amnestic effects of pharmacological agents administered after memory reactivation that target protein synthesis directly (e.g., Nader et al., 2000) or indirectly by targeting the release of neurotransmitters (e.g., norepinephrine) (e.g., Dębiec and LeDoux, 2004; Kindt et al., 2009). Those pharmacological studies have added greatly to our knowledge on the neurobiological mechanisms of memory reconsolidation. However, they do not provide us with information on whether and how daily life experiences can change the content and/or strength of previously formed memories. One potential candidate for such a naturalistic experience that may affect memory reconsolidation is stress exposure. Indeed, a real-life stressor (i.e., water deprivation) following memory reactivation enhanced contextual memory in the crab *chasmagnathus*, indicating that a naturalistic event may strengthen memory reconsolidation (e.g., Frenkel et al., 2005). Likewise, in humans it has been demonstrated that a stressful event can enhance reconsolidation of declarative memory (Coccoz et al., 2011, 2013; but see, Schwabe and Wolf, 2010). Confrontation with a stressful experience activates the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, which eventually leads to the release of catecholamines ((nor)adrenaline) and glucocorticoids. The hippocampus is critically involved in declarative memory processes and is highly sensitive to neuromodulators triggered during the stress response (Eichenbaum, 2004; Joëls and Baram, 2009). Thus, the finding that stress exposure affects memory reconsolidation may be explained by the effect of stress hormones on the neurocircuitry of reconsolidation.

Previous studies on the enhancing effect of stress exposure during the reconsolidation-window have focused on declarative memory for neutral information, whereas research on learning and memory (*consolidation*) demonstrate that stress exposure and stress hormones typically affect memory performance for emotional stimuli (e.g., Cahill et al., 2003; McGaugh, 2004). The sensitivity of emotional memory to stress effects can be explained by the observed interaction between emotion-induced arousal elicited by the emotional stimuli and the enhanced levels of stress hormones (Roozendaal et al., 2009). Whether stress also differentially affects *reconsolidation* of emotional and neutral memories is yet unknown. A previous study in humans suggests that post-reactivation stress may specifically enhance memory of emotional information (Marin et al., 2010). However, these results could not be ascribed to enhanced reconsolidation given that post-reactivation stress exposure improved recall performance at an immediate retention test, whereas the required protein synthesis for reconsolidation takes at least several hours (Walker et al., 2003; Duvarci and Nader, 2004). More insight in the interaction between post-retrieval stress exposure and memory performance may advance our understanding of why emotional memories are so persistent. Indeed, retrieval of traumatic memories is often accompanied by feelings of distress. This post-reactivation stress may strengthen the process of memory reconsolidation thereby facilitating the persistence of those memories.

Here, we tested in two experiments the effects of post-reactivation stress exposure on reconsolidation of emotional and neutral memories. Participants learned a list of neutral, positive and negative words. The next day, they received a reminder of the word list and were subsequently exposed to a stress task (i.e., social-evaluative cold pressor test, SECPT) (reactivation/stress group) or a control task (reactivation/no-stress group). To control for non-specific stress effects, an additional control group was solely exposed to the stress task on day 2, without memory reactivation (no-reactivation/stress group). On day 3, memory performance was assessed by means of a free recall task and a recognition task. Based on previous research of Coccoz et al. (2011), we expected that post-reactivation stress would improve memory performance in the reactivation/stress group compared to both control groups (reactivation/no-stress group and no-reactivation/stress group). Moreover, we expected that the enhancing effects of post-reactivation stress would be more pronounced for the emotional words (Marin et al., 2010).

2. Experiment 1

2.1. Methods

2.1.1. Participants

Seventy-three healthy participants (32 men and 41 women), ranging in age between 18 and 29 years, participated in study I. Self-reported medical and psychiatric problems or the use of medication known to influence the HPA-axis (except for oral contraceptives; $n = 35$) served as exclusion criteria. An additional exclusion criterion was a score above 18 on the Beck Depression Inventory (BDI) (Beck et al., 1996). Participants received either course credits or a small amount of money for their participation. The study was approved by the ethical committee of the University of Amsterdam and informed consent was obtained from all participants.

2.1.2. Design and general procedure

Fifty participants were randomly assigned to the reactivation/stress ($n = 25$) or reactivation/no-stress ($n = 25$) group.