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Cortisol response mediates the effect of post-reactivation stress exposure on contextualization of emotional memories

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Summary Retrieval of traumatic experiences is often accompanied by strong feelings of distress. Here, we examined in healthy participants whether post-reactivation stress experience affects the context-dependency of emotional memory. First, participants studied words from two distinctive emotional categories (i.e., war and disease) presented against a category-related background picture. One day later, participants returned to the lab and received a reminder of the words of one emotional category followed by exposure to a stress task (Stress group, $n = 22$) or a control task (Control group, $n = 24$). Six days later, memory contextualization was tested using a word stem completion task. Half of the word stems were presented against the encoding context (i.e., congruent context) and the other half of the word stems were presented against the other context (i.e., incongruent context). The results showed that participants recalled more words in the congruent context than in the incongruent context. Interestingly, cortisol mediated the effect of stress exposure on memory contextualization. The stronger the post-reactivation cortisol response, the more memory performance relied on the contextual embedding of the words. Taken together, the current findings suggest that a moderate cortisol response after memory reactivation might serve an adaptive function in preventing generalization of emotional memories over contexts.

1. Introduction

Threatening situations tend to be very well remembered. The ability to vividly remember contextual and specific cues that predict future catastrophes is highly adaptive. Accordingly, memories are generally better retrieved in their

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original encoding context than in unrelated situations (i.e., memory contextualization, Godden and Baddeley, 1975). When emotional memories generalize over contexts, they may become maladaptive and result in a disproportionate amount of fear and anxiety. Indeed, patients with post-traumatic stress disorder (PTSD) are hindered by superior memory for a traumatic event along with a reduced capacity to associate trauma-related cues to the trauma situation (Liberzon and Sripada, 2007). As a result, the trauma memory is retrieved and relived frequently, which causes an enormous amount of stress. The effect of this post-retrieval stress on emotional memory and specifically on memory contextualization is still largely unknown. Here, we address this issue by examining the role of post-retrieval stress on memory contextualization in healthy participants.

Upon retrieval, a memory trace enters a labile phase followed by a protein synthesis dependent restabilization phase, in which the memory trace is sensitive to change (Nader et al., 2000; Sara, 2000). The alleged functional role of this two-phased reconsolidation process is to keep our memories up to date by either altering their strength (Nader et al., 2000; Soeter and Kindt, 2010, 2011, 2012b) or incorporating new information into a memory trace (e.g., Forcato et al., 2007; Hupbach et al., 2007). A prerequisite to enter the reconsolidation window is that something can be learned during memory retrieval (e.g., Lee, 2009; Sevenster et al., 2013).

A naturalistic event that can affect memory reconsolidation is the experience of a stressor. Stress exposure activates the autonomic nervous system (ANS) and hypothalamus-pituitary-adrenal (HPA) axis, which eventually results in the release of catecholamines ((nor)adrenaline) and glucocorticoids (GCs). Previous studies in animals and humans show a complex interaction between stress and memory reconsolidation, in the sense that stress exposure or the administration of stress hormones can either *strengthen* memory reconsolidation (Frenkel et al., 2005; Coccoz et al., 2011; Gazarini et al., 2013; Bos et al., 2014) or *disrupt* memory reconsolidation (e.g., Tronel and Alberini, 2007; Maroun and Akirav, 2008; Zhao et al., 2009; Schwabe and Wolf, 2010). These apparently contradictory results may be explained by differences in experimental set-up, type of memory and the strength of the stress response.

It has been suggested that context can play an important role in triggering memory reconsolidation (Forcato et al., 2007; Hupbach et al., 2008; Forcato et al., 2009, 2010), but whether the context-dependency of memory is itself affected during reconsolidation is still unknown. The hippocampus is the key area for binding together multiple elements of an experience into a conjunctive representation (O'Reilly and Rudy, 2001) and for the contextual embedding of memories (e.g., Davachi, 2006). The hippocampus is also highly sensitive to stress hormones (Joëls and Baram, 2009). Previous studies on memory *consolidation* have shown that stress can affect memory contextualization in humans (van Ast et al., 2013, 2014), which is explained by the high sensitivity of the hippocampus to stress hormones (Joëls and Baram, 2009). The hippocampus is also involved in the process of reconsolidation (Debiec et al., 2002), specifically for context-specific memories (e.g., Winocur et al., 2009). Recent studies in humans and animals suggest that manipulations during the reconsolidation window not only affect the strength of the memory trace itself, but may affect the context-dependency of this memory trace as well (Winocur et al., 2009; Soeter and Kindt, 2012a, 2012b; Gazarini et al., 2013). We showed that pharmacological blockade of the noradrenergic system during the reconsolidation window diminished the subsequent fear response and that this fear-reducing effect generalized to a novel context (i.e. background)(Soeter and Kindt, 2012a). Furthermore, research in animals showed that pharmacological enhancement of the noradrenergic system during the reconsolidation window augmented the expression of fear, which generalized over contexts (Gazarini et al., 2013).

Here, we examined the role of post-reactivation stress exposure on the contextual dependency of emotional memories. In a mixed design, participants learned words from two distinctive emotional categories (i.e., war or disease) against a related background picture (i.e., war scene or hospital corridor, see Fig. 1). Approximately 24 h later, participants returned to the lab and were briefly reminded of the words of one emotional category. This procedure was intended to create a within-subject comparison between reactivated and non-reactivated words. Directly after the reminder procedure, half of the participants were confronted with a stress situation (Maastricht Acute Stress Test; MAST) whereas the other half of the participants received a non-stressful control task. Six days later participants returned to the lab and underwent a surprise word stem completion memory test wherein half of the word stems were presented against the original encoding context (i.e., congruent context) and half of the word stems were presented against the other context (i.e., incongruent context). Thus, in the congruent context condition the contextual information of the encoding situation was present, whereas in the incongruent context condition the contextual information was unrelated to the word to be generated. The difference in memory performance between the congruent and incongruent context provides an index for the contextual dependency of memory. We hypothesized that post-reactivation stress exposure would affect the contextual-dependency of declarative memory in humans. We left the direction of the memory contextualization effect open, given that we could argue either way. From a clinical point of view, we might expect that post-reactivation stress would *impair* the contextual-dependency of memories, whereas based on experimental observation we might expect that post-reactivation stress would *enhance* the contextual-dependency of memory (Winocur et al., 2009; van Ast et al., 2014).

2. Methods

2.1. Participants

Fifty-one healthy students from the University of Amsterdam (23 men and 28 women), ranging in age between 18 and 30 years ($M = 21.84$, $SD = 2.79$) participated in the study. Exclusion criteria were: a neurological or psychiatric condition, blood pressure (BP) >140/90, Beck Depression Inventory (BDI) score >18 (Beck et al., 1996), taking medication known to influence the HPA-axis and taking drugs on a regular basis, screened with the drug use disorder