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Cortisol mediates the effects of stress on the contextual dependency of memories

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Summary Stress is known to exert considerable impact on learning and memory processes. Typically, human studies have investigated memory for single items (e.g., pictures, words), but it remains unresolved how exactly stress may alter the storage of memories into their original encoding context (i.e., memory contextualization). Since neurocircuitry underlying memory contextualization processes is sensitive to the well-known stress hormone cortisol, we here investigated whether cortisol mediates stress effects on memory contextualization. Forty healthy young men were randomly assigned to a psychosocial stress or control group. Ten minutes after stress manipulation offset, participants were instructed to learn and remember neutral and negative words, each of which was depicted against a unique background picture. Approximately 24 h later, memory was tested by means of cued retrieval and recognition tasks. To assess memory contextualization half of the words were tested in intact item—contexts pairs, and half in rearranged item—context combinations. Recognition data showed that cortisol, but no other indices of stress such as heart rate or subjective stress, mediated the effects of stress on contextualization of neutral and negative memories. The mediation analysis further showed that stress resulted in increases in cortisol and that cortisol was positively related to memory contextualization, but unrelated to other measures of memory. Thus, there seems to be a specific role for cortisol in the integration of a central memory into its surrounding context.

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1. Introduction

Memory retrieval is generally enhanced when the encoding context and retrieval context are similar (Godden and Baddeley, 1975). As such, the ability to store declarative memories into their original encoding context (i.e., memory *contextualization*) is highly adaptive since it aids in subsequently retrieving memories that are likely to be appropriate in a specific context. The hippocampus has been suggested to underlie context effects on memory (e.g., O'Reilly and Rudy, 2000), by binding together multiple elements of an experience into a novel conjunctive representation (O'Reilly and Rudy, 2000; Eichenbaum, 2004). Also, the hippocampus is known to be sensitive to corticosteroids (de Kloet et al., 2005) that are released from the adrenal cortex in response to stress. Thus, by means of stress hormone effects on memory neurocircuitry, stress may affect the contextualization of memories. However, as of yet, little research with humans has examined how stress influences memory contextualization processes. Instead, studies focused on single items to be memorized, such as words or pictures. Because memories are often interrelated in complex associative networks rather than stored in isolation, investigating the effects of stress on memory contextualization might be a more ecological valid approach to investigating stress effects on memory.

Animal research has shown that glucocorticoid receptor (GR) activation by cortisol seems to be a prerequisite for the storage of information (de Kloet et al., 2005). In humans, stress typically enhances consolidation (Buchanan and Lovallo, 2001), and can enhance encoding (Cornelisse et al., 2011; de Quervain et al., 2009; but see Elzinga et al., 2005; Van Ast et al., 2013a). Such alterations in memory have indeed been shown to positively relate to stress-induced cortisol levels (e.g., Smeets et al., 2008; Cornelisse et al., 2011). Thus, one might predict that stress enhances memory contextualization. However, enhanced *item* memory (e.g., pictures, words) by stress does not necessarily mean that binding the item into its original encoding context will be enhanced as well. In agreement, the 'arousal-impairs-binding' theory (Payne et al., 2003), poses that stress (likely through corticosteroid effects) enhances memory for item information from an arousing event at the cost of contextual binding, since these two types of memory formation depend upon different brain regions that on their turn differ in their sensitivity to corticosteroids (see also Mather, 2007).

Context has been broadly defined as the internal (cognitive and hormonal) and external (environmental and social) background against which psychological processes operate (Spear, 1973). Consequently, previous studies investigating the effects of stress on contextual binding have operationalized context in various ways. One study demonstrated that social stress enhanced memory for words related to personality, but not a category unrelated to personality, which was interpreted as enhanced context congruent memory by stress (Smeets et al., 2007). Another study found that stress enhanced memory for the stress manipulation itself (Quas et al., 2010), but here context was not explicitly manipulated, neither was an appropriate control group included, precluding causal conclusions on the role of stress in the contextualization of memory. Notably, stress effects in both studies were positively related to cortisol. Another study manipulated thematic arousal independently of the to-be remembered material, and showed that social stress specifically enhanced high arousing themes. In addition, this memory-enhancing effect was most pronounced for elements central to the to-be-remembered event (Echterhoff and Wolf, 2012), which was again positively associated with cortisol. Confirming a crucial role for cortisol in memory contextualization, we have shown that cortisol may enhance or impair memory contextualization, depending on the timing of cortisol elevations relative to memory encoding (Van Ast et al., 2013b). Other studies did not report possible relationships of cortisol with stress effects on contextual dependency of memory. One study manipulated context by the physical environment in which encoding and retrieval took place (i.e., change of room and odor) and found that stress impaired the typical memory enhancement by context congruency (Schwabe et al., 2009). A second study showed that social stress enhanced memory for objects that were central to the stressor, but not for unrelated items (Wiemers et al., 2013).

Summarizing the above findings, cortisol likely plays an important role in the relationship between stress and memory contextualization. Therefore we hypothesized that cortisol may *mediate* the effects of stress on memory contextualization. This effect may be most pronouncedly observed in negative (i.e., of negative valence) memories as compared to neutral memories, by means of glucocorticoid modulation of emotion-induced noradrenergic activation (Roozendaal et al., 2006). Since the direction of cortisol effects on contextualization is still debatable, and previous studies have reported mixed results (Smeets et al., 2007; Schwabe et al., 2009; Echterhoff and Wolf, 2012; Van Ast et al., 2013b; Wiemers et al., 2013), we left the direction of cortisol effects on contextualization open. We used mediation analysis (Baron and Kenny, 1986; Shrout and Bolger, 2002; see also Fig. 1A) since it is a powerful method to assess whether cortisol explains a substantial amount of the covariance between stress and the extent to which a stimulus is remembered in a context-dependent manner. In addition, given that profound individual differences exist in memory performance as well as in (psycho)physiological responses to stress, mediation analysis is preferable over methods that merely test for group differences (Kosslyn et al., 2002). To critically test a unique role for cortisol in mediating stress effects on memory contextualization, we also tested whether other indices of stress such as heart rate, heart rate variability (HRV; an index of adaptive regulation of peripheral control: Thayer et al., 2012), alpha amylase (i.e., a marker of noradrenergic activity) or subjective mood functioned as mediators. Memory performance was assessed by cued retrieval and recognition tasks. Recognition performance is thought to originate from two independent memory processes; it may either be based on a detailed vivid feeling of reexperience (recollection), or on a sense that the item has been previously encountered (a sense of familiarity; Yonelinas, 2002). Therefore, we also tested whether cortisol mediated either of these processes specifically.

2. Methods

2.1. Participants

Forty male participants participated in the experiment with a mean age of 22 years (SD = 3.76, 18—39) and mean BMI of