# Time-Dependent Effects of Cortisol on the Contextualization of Emotional Memories

Vanessa A. van Ast, Sandra Cornelisse, Martijn Meeter, Marian Joëls, and Merel Kindt

**Background:** The inability to store fearful memories into their original encoding context is considered to be an important vulnerability factor for the development of anxiety disorders like posttraumatic stress disorder. Altered memory contextualization most likely involves effects of the stress hormone cortisol, acting via receptors located in the memory neurocircuitry. Cortisol via these receptors induces rapid nongenomic effects followed by slower genomic effects, which are thought to modulate cognitive function in opposite, complementary ways. Here, we targeted these time-dependent effects of cortisol during memory encoding and tested subsequent contextualization of emotional and neutral memories.

**Methods:** In a double-blind, placebo-controlled design, 64 men were randomly assigned to one of three groups: 1) received 10 mg hydrocortisone 30 minutes (rapid cortisol effects) before a memory encoding task; 2) received 10 mg hydrocortisone 210 minutes (slow cortisol) before a memory encoding task; or 3) received placebo at both times. During encoding, participants were presented with neutral and emotional words in unique background pictures. Approximately 24 hours later, context dependency of their memories was assessed.

**Results:** Recognition data revealed that cortisol's rapid effects impair emotional memory contextualization, while cortisol's slow effects enhance it. Neutral memory contextualization remained unaltered by cortisol, irrespective of the timing of the drug.

**Conclusions:** This study shows distinct time-dependent effects of cortisol on the contextualization of specifically emotional memories. The results suggest that rapid effects of cortisol may lead to impaired emotional memory contextualization, while slow effects of cortisol may confer protection against emotional memory generalization.

**Key Words:** Consolidation, context, cortisol, emotion, hydrocortisone, memory, PTSD

Memories are more likely to be remembered when the retrieval context resembles the encoding context (1–3). Such contextual dependency of memories is highly adaptive, as it can help to retrieve memories that are likely to be appropriate in a specific context. Consequently, the ability to store memories into their original encoding context (i.e., memory contextualization) may protect against memory generalization. Since patients suffering from posttraumatic stress disorder (PTSD) display augmented memory generalization (4), contextualization of emotional memories seems to be compromised in PTSD (5–8). The hippocampus, which is supposed to subserve context effects on memory (9–12), is a main target of the stress hormone cortisol (13). Through its effects on the hippocampus, cortisol may impair the contextual dependency of memories, but whether this is indeed the case in healthy humans is presently unknown. In general, the literature on the potential role of cortisol in (traumatic) memory formation is equivocal. For instance, one recent animal study showed that corticosteroids, injected after fear conditioning, reduce context-specific fear responses the next day, causing PTSD-like symptoms (14). Conversely, another study showed that corticosteroid administration before acute stress could dampen subsequent behavioral characteristics of PTSD (15).

One possible explanation for such paradoxical effects of corticosteroids is that these hormones exert time-dependent effects on neurobiological processes, with disparate net effects on behavior (16–20). After a stressful event, nongenomic corticosteroid actions quickly enhance neural activity mediated by glutamate in mice, particularly in the amygdala (21,22). In humans, acutely elevated cortisol levels generally suppress hippocampal activity (23–25). In interaction with noradrenergic activation, corticosteroids (via rapid actions) enhance human amygdala activity (26–29) and facilitate instinctive, habitual behavior (30) and negative response biases (31,32), while impairing higher order controlled executive processes (33). Together, these behaviors may promote survival at the short term, helping the organism to select the most appropriate strategy immediately after stress, though at the cost of remembering contextual details. Some hours after stress, slower long-lasting genomic corticosteroid actions develop (16,34). The available data suggest that these slow actions serve to restore homeostasis following stressful periods (20,35,36). In agreement, slow corticosteroid effects have been shown to enhance cognitive self-control (37), enhance working memory processing involving the dorsolateral prefrontal cortex (38), promote sustained attentional processing (39), and reduce amygdala activity (39,40). As such, slower genomic corticosteroid effects may aid in remembering a certain event in a more cognitively controlled, contextualized, manner.

Given these findings, we probed these two time domains and tested the hypothesis that rapid cortisol effects [presumably through nongenomic pathways and in interaction with arousal-evoked central adrenergic release caused by the emotional words (41,42)] impair the contextual dependency

From the Department of Clinical Psychology (VAvA, MK), University of Amsterdam, Amsterdam; Department of Neuroscience and Pharmacology (SC, MJ), Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht; Amsterdam Brain and Cognition (SC, MJ, MK), University of Amsterdam, Amsterdam; and Department of Cognitive Psychology (MM), VU University Amsterdam, Amsterdam, The Netherlands.

Address correspondence to Vanessa A. van Ast, M.Sc., University of Amsterdam, Department of Clinical Psychology, Weesperplein 4, Room 5.19, Amsterdam 1018 XA, Netherlands; E-mail: V.A.vanAst@uva.nl.

Received Nov 27, 2012; revised Jun 27, 2013; accepted Jun 29, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.06.022

specifically of emotional memories and that delayed (presumably gene-mediated) effects of cortisol enhance contextual dependency of subsequent emotional memories. To test this, we randomly assigned healthy young men to one of three groups: 1) a group receiving placebo at 210 minutes and 10 mg hydrocortisone at 30 minutes before encoding (rapid cort); 2) a group receiving cortisol 210 minutes and placebo 30 minutes before encoding (slow cort); and 3) a group receiving placebo at both times. During encoding, participants were presented with neutral and emotional (i.e., of negative valence and high arousal) words in unique background pictures. Approximately 24 hours later, memory contextualization was assessed; half of the emotional and neutral words were tested in intact contexts, while the other half of the words were tested in rearranged context combinations (43,44). In addition to objective alterations in memory performance, we conducted exploratory analyses to test for changes in the subjective quality of memories (45).

## Methods and Materials

### Participants

In total, 64 male subjects gave written informed consent. Participant characteristics are given in the Supplementary Results in Supplement 1. The local ethical committee of the University of Amsterdam approved the study. Inclusion criteria as assessed by self-report were no past or present psychiatric or neurological condition, no diagnosis of dyslexia, and age between 18 and 35 years. Men having any somatic or endocrine disease (e.g., acute asthma) or taking any medication known to influence central nervous system or endocrine systems were excluded from participation. A final exclusion criterion constituted nonadherence to the encoding instructions on day 1. Further, participants were asked to refrain from taking any drugs 3 days before participation and to get a night of proper sleep, refrain from heavy exercise and alcohol and caffeine intake 12 hours before participation, and to not eat, drink, smoke, or brush teeth 2 hours before participation. Subjects were rewarded for their participation with course credits or paid €65.

### Drug Administration and Assessment

Hydrocortisone and placebo (albochin) treatments were administered through identically appearing pills. A single dose of 10 mg of hydrocortisone was employed to elevate endogenous cortisol to a level equivalent to moderate acute stress (46). Salivary free cortisol concentrations were assessed with Salivette collection devices (Sarstedt, Nümbrecht, Germany). Cortisol samples were taken at 10 time points spread throughout the experiment (Figure 1) and subsequently stored at −25°C. Upon completion of the study, samples were sent out to Dresden (Technische Universität, Germany) where salivary free cortisol concentrations were measured using a commercially available chemiluminescence immunoassay with high sensitivity of .16 ng/mL (IBL, Hamburg, Germany).

### Memory Measurements

**Encoding.** The encoding task was modeled freely after Talamini *et al.* (43) and Tambini *et al.* (44). To induce emotional versus neutral declarative memories, participants were shown 30 neutral, low-arousing words and 30 negative, high-arousing words on a small gray rectangle presented against color pictures of natural scenes or city landscapes (Figure 2). We utilized words because they are easier than pictures to match on a range of dimensions (e.g., frequency or familiarity) that affect memory performance (47). Furthermore, memory-enhancing effects for arousing words are likely mediated by rapid arousal-evoked central adrenergic release from the locus coeruleus (48) mediated by the amygdala (41,42). Subjects were instructed to vividly imagine the meaning and content of each word in the background 1) to promote deep encoding (49), 2) to create an association of the word with its unique context, and 3) to create a complete and rich episodic memory. Each individual word was presented for 5 seconds together with a unique context in random order. Next, participants evaluated their mental image on arousal and valence dimensions using self-assessment manikins (50) in a fixed time window of 4 seconds for each rating. In between trials, a fixation cross was presented for 1 second. Words were concrete nouns drawn from a validated database (51), consisted of 5 to 10 letters, and contained no more than three syllables. All words were balanced, so that the emotional and

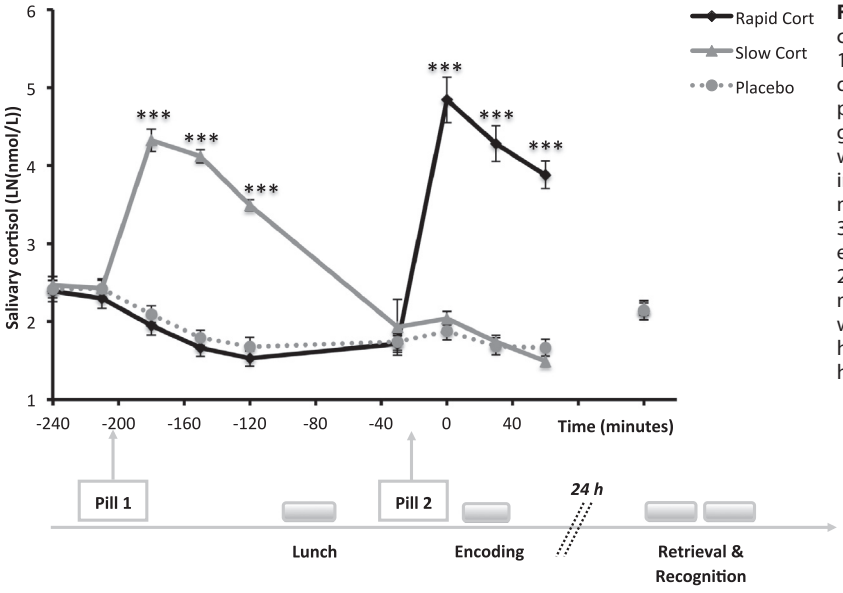


**Figure 1.** Overview of the experimental design and salivary cortisol curves. Participants received a pill 210 minutes (pill 1) and 30 minutes (pill 2) before memory encoding (t = 0) at day 1 that could contain 10 mg hydrocortisone (Cort) or placebo (albochin). Hydrocortisone administration in both groups significantly elevated salivary cortisol as compared with placebo but did not differ immediately before each pill intake or during baseline at day 2. Throughout the experiment, saliva samples were taken at 240, 210, 180, 150, 120, 30, and 0 minutes before encoding; 30 and 60 minutes after encoding; and before the surprise recall and recognition test 24 hours later. Error bars represent standard error of the mean (SEM). Significant Bonferroni corrected differences with placebo are depicted by ***$p < .005$. Rapid Cort; hydrocortisone 30 minutes before encoding, Slow Cort; hydrocortisone 210 minutes before encoding.