



SHORT COMMUNICATION

Autobiographic memory impairment following acute cortisol administration

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Summary Previous experimental studies in humans have reported that the administration of cortisol impairs retrieval of hippocampal dependent, episodic memory. In particular, cortisol impaired recall of previously learnt words. In the present study, we investigated if cortisol also affects autobiographical memory, which reflects a subcategory of hippocampal dependent, episodic memory. Twenty two male students participated in this placebo-controlled, double-blind crossover study. One hour after the administration of 10 mg hydrocortisone, subjects generated significantly fewer specific memories in the Autobiographical Memory Test (AMT) when compared to placebo. In contrast, cortisol did not affect mood and attention. The present findings extend the current knowledge about cortisol effects on memory retrieval and raise the possibility that impaired autobiographical memory in depression may be at least partly due to elevated cortisol levels which often accompany this disorder.

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1. Introduction

There is evidence from animal studies that acute stress modulates memory, with enhancing and impairing effects being reported (de Kloet et al., 1999; Roozendaal, 2002). Stress associated with learning of a task facilitates memory consolidation. Studies in rats suggest that this effect is mediated by activated glucocorticoid receptors (GRs) and depends on a co-activation of β -adrenergic receptors in the basolateral nucleus of the

amygdala (BLA; Roozendaal, 2002). Studies with mouse mutants have further revealed that binding of the GRs to DNA in the hippocampus is required for this effect (Oitzl et al., 2001). In humans, following the administration of hydrocortisone, memory is enhanced for emotionally arousing material but not for neutral information (Buchanan and Lovallo, 2001), which is in line with the above mentioned animal results supporting an involvement of the amygdala in the cortisol effect on consolidation.

In contrast stressors unrelated to the learning event (out of context) can impair spatial memory in rats (Diamond et al., 1996). Experimental studies in healthy human subjects have also observed

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that psychosocial stress or acute cortisol treatment often has impairing effects on declarative memory (Lupien and McEwen, 1997; Wolf, 2003). Recent studies have found that acute glucocorticoid treatment leads to impaired recall of previously learnt material in animals (de Quervain et al., 1998) and humans (de Quervain et al., 2000; Wolf et al., 2001). Hippocampal GRs are assumed to mediate this cortisol memory effect, which is supported by recent animal data indicating that selective hippocampal glucocorticoid receptor activation leads to impaired spatial memory retrieval (Roosendaal et al., 2003). Moreover, a human neuroimaging study of memory retrieval reported reduced blood flow in the medial temporal lobe after cortisone administration, which was accompanied by impaired memory retrieval (de Quervain et al., 2003).

Autobiographical memory is conceptualised as a subsystem of episodic memory, being responsible for remembering specific episodes of one's own past (Tulving, 2002). Impaired autobiographic memory performance in depressed patients is characterized by their inability to recall specific individually experienced events, but answering with summary descriptions of situations instead (Barnhofer et al., 2002). In patients with major depression, hyperactivity of the hypothalamus pituitary adrenal (HPA) axis leading to hypercortisolemia is a frequently observed abnormality (Parker et al., 2003). No cortisol measurements were conducted in the Barnhofer's study, so that it is not clear if the autobiographic memory deficits were associated with hypercortisolism. Speculating that the autobiographic memory impairment in depressed patients could be associated with their hypercortisolemic state, we were interested to study the effects of acute hydrocortisone administration on autobiographic memory (AM) retrieval in healthy subjects.

2. Methods and material

Twenty-two healthy male university students (mean age 26.27 ± 0.89) participated in this double-blind, placebo-controlled, crossover study. All participants were free of medication at the time of testing. The study was approved by the local ethics committee, and all subjects gave written informed consent. Each participant was tested twice with parallel versions of the autobiographic memory test (AMT). A dose of ten milligrams of hydrocortisone (Hoechst) or placebo was administered orally 1 hour prior to memory testing, which took place between 15:30 and 17:30 h. The treatment condition was randomly assigned to the two testing days between which the interval ranged

between 3–7 days. Salivary samples were obtained using Salivette sampling devices (Sarstedt Germany) before drug intake and 60 mins (before memory testing) thereafter. Free cortisol in these samples was determined by a time-resolved immunoassay with time-resolved fluorometric detection.

2.1. Tests and questionnaire

A modified version of the autobiographic memory cueing test was used (Williams and Broadbent, 1986). It consisted of two parallel versions that contained two positive, two negative and two neutral adjectives each, that were found to be effective to initiate memory retrieval of the according valence (see appendix for the adjective lists). Both versions of the AMT were presented to each participant, with the two versions being counterbalanced across the two treatment conditions. The participants were instructed verbally and in written form to write down a specific event from their own past in response to the provided adjectives. They were told that solely the specificity of the event was important, not its content. Subjects were instructed to recall a specific actual experience and not to confabulate an event. They were told to recall an event that took place at a certain place and did not last any longer than one day. Additionally they were provided with an example of a specific and an unspecific answer. The answers of the subjects could not be verified by an external source (e.g. a proxy). To evaluate the dependent variable "specificity of the given answer" two trained raters, blind to the subjects' treatment, evaluated independently whether an answer was specific or general. An answer was considered specific when at least two of the following criteria were met: description of the location (e.g. at home, in church etc.), the point of time (e.g. Sunday morning, my birthday etc.) and the persons involved. The score 1 was given for each specific answer and the score 0 was given for non-specific answers. Since there were two positive, two negative and two neutral adjectives in each test version, the maximal score for the number of specific events was two for each valence category. For the scoring a high inter-rater reliability was obtained ($\text{r} > 0.82$). The mean of the two raters' sum score was used as test score.

Potential glucocorticoid effects on mood were assessed with a German adjective list, which contained three scales for elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness (Steyer et al., 1997). In addition attention was measured using a timed cancel-

lation task, where subjects were supposed to mark previously defined letters out of a row of similar looking distractor letters (Brickenkamp, 2001).

Effects of hydrocortisone on memory, mood and attention performance were evaluated using *t*-tests for paired samples.

3. Results

3.1. Cortisol levels

The participants showed a significant increase ($t_{(21)} = -4.45, p < 0.0001$) in free cortisol one hour after administration of 10 mg hydrocortisone (mean \pm SEM: 99.13 ± 20.44 nmol/l) when compared to their baseline levels (10.01 ± 0.74 nmol/l).

3.2. Cognitive tests

Following hydrocortisone administration retrieval performance in the AMT was significantly impaired ($t_{(21)} = -3.59, p = 0.002$) indicated by fewer specific memories (4.45 ± 0.35) than following placebo administration (5.22 ± 0.23). A within-subject ANOVA revealed no significant interaction between the treatment and the three emotional categories ($F_{(20)} = 1.55, p = 0.24$). For exploratory reasons we calculated single *t*-tests for the three categories. These showed that cortisol only impaired retrieval of neutral ($t_{(21)} = -3.14, p = 0.005$) events, while having no effect on retrieval of positive ($t_{(21)} = -1.48, p = 0.154$) and negative events ($t_{(21)} = -1.67, p = 0.11$) (see Fig. 1).

Cortisol administration did not significantly influence mood and attention as verified by non-significant mean differences in the according tests

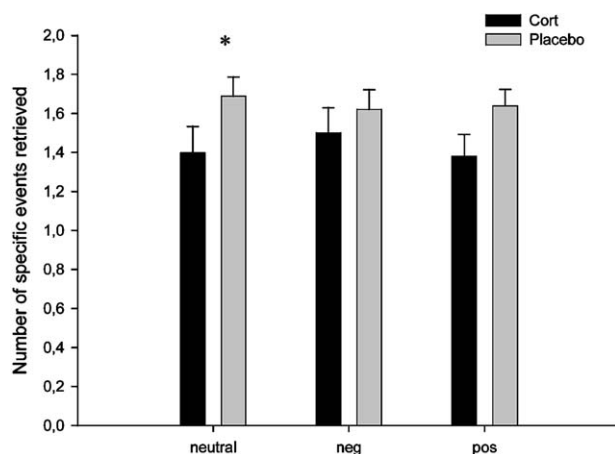


Fig. 1. Effects of cortisol administration on specific positive, negative and neutral episodes retrieved during the autobiographic memory test.

(data not shown). In addition participants self reported not to have noticed when they had received which treatment.

4. Discussion

Previous experimental studies in humans have reported that recall of words (declarative memory) is impaired after cortisol administration (de Quervain et al., 2000; Wolf et al., 2001). The current study extends these findings to the domain of autobiographical memory. The hippocampus has been considered to play a crucial role in both the storage and retrieval of information, and the individual's orientation within a given spatial, temporal and subjective environment (Hellhammer, 1983; Nadel et al., 2000). Thus, the hippocampus may be a possible candidate for mediating the cortisol effects on autobiographical memory. More definite information about the localization of this memory effect could be gained from a neuroimaging study.

Autobiographic memory impairments are also observed in depressed and suicidal patients (Williams and Broadbent, 1986; Barnhofer et al., 2002). Depression is often accompanied by cortisol hypersecretion (Parker et al., 2003). On the basis of the present results it is possible that the autobiographic memory impairment in depression is in part due to glucocorticoid effects. It is important to note though that the chronic hypercortisolemic state in depressed patients cannot easily be compared to the acutely risen cortisol levels in this healthy group since negative long-term consequences like hippocampal atrophy are not present. Taking this into consideration it is even more impressive that high cortisol levels per se are able to induce such impairments for autobiographic memory retrieval. Although only found in an exploratory analysis, it is interesting to note that the glucocorticoid effects are more pronounced in the retrieval of neutral events while the retrieval of positive and negative events was not significantly affected. In line with results suggesting better memory consolidation when cortisol is elevated and the BLA is activated (Buchanan and Lovallo, 2001; Roozendaal, 2002) the missing cortisol effect on the retrieval of emotional memories could be due to a stronger consolidation of those arousing events.

In sum, this is the first experimental study to report effects of an acute pharmacological cortisol elevation on autobiographical memory retrieval in healthy male subjects. The current results extend previous studies observing cortisol

induced impairments in declarative (episodic) memory retrieval. Whether autobiographical memory impairment in psychiatric patients is related to their hypercortisolemia and/or changes after successful treatment awaits to be determined in future studies.

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Appendix

Adjectives used in the two parallel versions of the AMT (translated from German).

	Positive	Negative	Neutral
Version A	happy interested	angry hurt	concentrated busy
Version B	safe successful	sad clumsy	patient correct

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