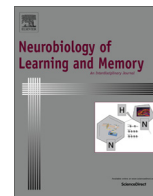




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## Differential effects of acute cortisol administration on deep and shallow episodic memory traces: A study on healthy males



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### ABSTRACT

We aimed at investigating rapid effects of plasma cortisol elevations on the episodic memory phase of encoding or retrieval, and on the strength of the memory trace. Participants were asked either to select a word containing the letter “e” (shallow encoding task) or to judge if a word referred to a living entity (deep encoding task). We intravenously administered a bolus of 20 mg of cortisol either 5 min before encoding or 5 min before retrieval, in a between-subjects design. The study included only male participants tested in the late afternoon, and neutral words as stimuli. When cortisol administration occurred prior to retrieval, a main effect of group emerged. Recognition accuracy was higher for individuals who received cortisol compared to placebo. The higher discrimination accuracy for the cortisol group was significant for words encoded during deep but not shallow task. Cortisol administration before encoding did not affect subsequent retrieval performance (either for deep or shallow stimuli) despite a facilitatory trend. Because genomic mechanisms take some time to develop, such a mechanism cannot apply to our findings where the memory task was performed shortly after the enhancement of glucocorticoid levels. Therefore, glucocorticoids, through non-genomic fast effects, determine an enhancement in episodic memory if administered immediately prior to retrieval. This effect is more evident if the memory trace is laid down through deep encoding operations involving the recruitment of specific neural networks.

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### 1. Introduction

Glucocorticoids exert their actions directly on brain regions, including the hippocampus, amygdala and prefrontal cortex that are enriched in glucocorticoid receptors and are important for long-term memory formation (de Kloet, Oitzl, & Joels, 1999). Evidence has emerged for rapid, non-genomic and transient effects of these receptors when expressed at the cell membrane in different brain areas (de Kloet, Karst, & Joels, 2008). In the hippocampus, lower-affinity membrane-associated mineralocorticoid receptors were reported to be located presynaptically and to rapidly increase glutamate release probability upon activation by moderate-to-high glucocorticoid doses (Joels, Karst, DeRijk, & de Kloet, 2008). They were also implicated in the fast-inducing actions of cortisol in

medial prefrontal cortex-dependent cognition (Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010). The effects of acute action of intravenous glucocorticoids administration on memory functions can be quite divergent: both facilitation of memory trace formation (or encoding) and impairment of its recall (retrieval) (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Sandi & Pinelo-Nava, 2007) have been described. Several influential models have accommodated such contradictory findings by classifying effects according to the characteristics of the glucocorticoids response and/or the memory process under study (de Quervain, Aerni, Schelling, & Roozendaal, 2009; Joels, 2006; Joels et al., 2006; Roozendaal, 2002). Recently, a comprehensive model that incorporates principles related to the ‘timing’ (with regards to the cognitive challenge) and the ‘dosage’ of glucocorticoids administration, as well as to the characteristics of the neural recruitment triggered by the cognitive challenge, has been proposed (Sandi, 2011). This model also emphasises the relevance of the coupling between glucocorticoids elevation and neural activity related to

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information processing for the cognitive outcome. According to the model: (i) Facilitating effects on memory processes are observed when moderate-to-high glucocorticoids elevations coincide with the timing of the information processing. Specifically, memory processes are facilitated by glucocorticoids elevation (triggered by the task or induced by exogenous administration) that takes place over a time-period extending from shortly before training (i.e. less than 5 min before) to up to 1 h after training (Akirav et al., 2004; Sandi, Loscertales, & Guaza, 1997). These circumstances foster both rapid and delayed (protein-synthesis dependent) mechanisms/processes. In general, rapid effects are mediated by membrane-bound mineralocorticoid (MR) or glucocorticoid (GR) receptors whereas delayed genomic effects are mediated by MR and GR receptors located in the cytosol which move into the nucleus upon activation in order to affect gene expression. (ii) Detrimental effects on memory processes are observed when high-to-very high glucocorticoids elevations occur in an uncoupled manner during a time-window (10–60 min before, but not at shorter time points) preceding the cognitive challenge (de Quervain, Roozendaal, & McGaugh, 1998; Wong et al., 2007). Although these mechanisms are predominantly related to the detrimental effects of stress and glucocorticoids on retrieval (Wong et al., 2007), under similar uncoupled conditions, glucocorticoids treatments can also impair memory formation (Joels et al., 2006). (iii) The nature of the cognitive challenge – and, in turn, the recruited neural circuitries and networks – is a key determinant of glucocorticoids action on cognition.

Episodic memory is concerned with conscious recollection of previous experiences, either in association with an emotion or not, as a series of perceptual and semantic representations of objects that interact in space and time within a larger spatio-temporal context (Mayes & Roberts, 2001). In episodic memory research, it is possible to access different levels of processing (i.e., deep and shallow) by using two kinds of learning context (semantic and perceptual features). The most common explanation for level-of-processing effects is that deep study processing leaves behind semantically more elaborate memory traces than shallow processing. Because most episodic recognition tests typically induce participants to rely on semantic, associative, information to retrieve the encoding episode, deep processing leads to better performance than shallow processing over a wide range of episodic memory tests (Craik, 2002). This allows to address possible differences in task sensitivity involving the interplay between different brain regions (Brown & Aggleton, 2001; Buckner & Wheeler, 2001; Rugg & Yonelinas, 2003) and the degree of neural recruitment of relevant cognitive networks engaged by the recognition task. Several neuroimaging studies have demonstrated that the prefrontal cortex and the hippocampus are implicated in deep and shallow encoding (Baker, Sanders, Maccotta, & Buckner, 2001; Fletcher, Stephenson, Carpenter, Donovan, & Bullmore, 2003; Otten, Henson, & Rugg, 2001). Functional studies have established that deep encoding has neural correlates in the left prefrontal cortex (Innocenti et al., 2010; Kohler, Paus, Buckner, & Milner, 2004), while specific effects for shallow encoding have been found in posterior brain regions (Otten et al., 2001; Schott et al., 2013).

In the present study, we aimed at investigating whether episodic memory was influenced by rapid effects of plasma cortisol elevations following exogenous administration shortly before either encoding or retrieval. A level of processing approach was used in order to assess whether cortisol had differential effects according to the strength of the cognitive challenge resulting in different strength of the memory trace. This information is of crucial relevance, as several psychopharmacological studies have demonstrated that the effects of pharmacological administration on recognition memory largely depend upon depth of encoding (Bentley, Driver, & Dolan, 2009; FitzGerald et al., 2008; Honey et al., 2005). Consequently, any comprehensive account of drug-

induced effects on memory should consider that the effects may vary according to the specific cognitive strategies used to lay down the memory trace. We intravenously administered a bolus of 20 mg of cortisol, causing a rapid elevation of cortisol plasma levels, either 5 min before encoding or 5 min before retrieval, in a between-subjects design. This timing was chosen as it coincides with the onset of facilitatory changes in cortical excitability in humans by fast, non-genomic effects (Milani et al., 2010).

## 2. Methods

### 2.1. Subjects

Thirty-two healthy males took part in the study (mean age,  $M = 33$  years, standard deviation,  $SD = 11$  years, range 21–62 years). Females were excluded to avoid potential confounds due to variations of ovarian hormones levels (Smith, Adams, Schmidt, Rubinow, & Wassermann, 2002). Participants reported to be right-handed, have normal or corrected-to-normal vision, and not to have history of neurologic or psychiatric diseases. Subjects with abnormal sleeping patterns or using sleep-inducing drugs were excluded from the sample. In order to assess any effect of cortisol administration before encoding and retrieval, participants were randomly assigned to four groups of eight participants each, with the restriction that the age-range of participants in each group was approximately the same and mirrored the age-range of the whole sample. Participants in the first two groups received intravenous administration of cortisol (20 mg) or saline solution (same quantity) 5 min before the encoding phase (encoding/cortisol and encoding/placebo groups, respectively), and no substance before the retrieval phase. Participants in the two remaining groups received cortisol or saline solution before the retrieval phase (retrieval/cortisol and retrieval/placebo groups), while the encoding phase was carried out without substance administration. The four groups did not differ in age (one-way analysis of variance,  $p = 0.972$ ). Written informed consent was obtained from all participants. The study was approved by the Local Ethic Committee, and the procedures were in accordance with the Declaration of Helsinki.

### 2.2. Procedure

We used a double-blind, placebo-controlled between-subjects design.

Participants in the two cortisol groups (encoding or retrieval) received an intravenous bolus of 20 mg of cortisol. This dose, which is just below the median dose used in cognitive studies (Het, Ramlow, & Wolf, 2005), is able to yield a substantial and lasting increase of plasma cortisol concentrations that are within physiological limits and, to significantly increase corticospinal and motor cortical excitability from 5 min to 25 min after the injection (Milani et al., 2010) which is enough for completing the encoding/retrieval phases. Participants in the placebo groups received an intravenous bolus of 0.2-mL of saline solution. Administration of cortisol or saline solution occurred 5 min before the start of the encoding or the retrieval task, depending on the group. All participants were tested in the afternoon between 4.00 and 5.00 pm to minimize variability in the endogenous production of cortisol (Ranjit, Young, Raghunathan, & Kaplan, 2005).

The experimental protocol involved an incidental encoding phase, followed by a retrieval phase approximately 24 h later. The procedure was identical for all participants, and already used to causally investigate prefrontal neural circuitries involved in deep and shallow memory tasks (Innocenti et al., 2010). Subjects sat in a comfortable chair in front of a 17-in monitor. In the encod-

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