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

David Cioncoloni [a,b], Giulia Galli [c], Riccardo Mazzocchio [c,*], Matteo Feurra [c], Fabio Giovannelli [d], Emiliano Santarnecchi [c], Marco Bonifazi [e], Alessandro Rossi [c,e], Simone Rossi [c]

[a] U.O.P. Professioni della Riabilitazione, Azienda Ospedaliera Universitaria Senese, Siena, Italy
[b] Scuola di Dottorato in Scienze Cognitive, Università di Siena, Italy
[c] Neurologia e Neurofisiologia Clinica, Dipartimento di Scienze Neurologiche e Neurosensoriali, Azienda Ospedaliera Universitaria Senese, Siena, Italy
[d] Unità di Neurologia, Azienda Sanitaria di Firenze, Ospedale San Giovanni di Dio, Florence, Italy
[e] Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze, Università di Siena, Italy

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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.

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

* Corresponding author. Address: Viale Bracci, I-53100 Siena, Italy. Tel.: +39 0577 233409; fax: +39 0577 40327.
E-mail address: mazzocchio@unisi.it (R. Mazzocchio).

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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 contest (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, & Bullmorel, 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-

ing phase, participants viewed a series of words. Words were 80 Italian nouns of common use (according to the Corpus and Frequency Lexicon of Written Italian CoLFIS, http://www.istc.cnr.it/material/database/colfis/), ranging between four and twelve letters in length. They were presented one at a time on the monitor, with white font colour on a black background. The presentation of the words was divided into four blocks of 20 stimuli each, and the order of blocks was randomised across participants. In two blocks, participants were requested to decide whether or not the word was animate (or referred to the property of a living entity). This task has been used in previous studies to engage deep, semantic encoding operations (Otten, Henson, & Rugg, 2002). In the other two blocks, participants were asked to judge whether or not the word contained the letter 'e' to engage shallow, perceptual encoding operations. In each block of the deep encoding task, half of the words referred to a living entity, whereas in each block of the shallow encoding task half of the words contained the letter 'e'. Participants were instructed to press the left button of the mouse with their index finger if they thought the word was animated (for the deep task) or contained the letter 'e' (for the shallow task), and to press the right button with their middle finger if the word was inanimate or did not contain the letter 'e'. The instructions emphasised response speed as well as accuracy. Only after completing the encoding task were participants informed about the subsequent memory test.

Twenty-four hours later, participants performed a retrieval test. In choosing the experimental paradigm for testing the acute effects of cortisol on episodic memory retrieval, several issues were considered. *The type of cognitive process*, i.e., retrieval may be vulnerable to elevated glucocorticoids (Howland & Cazakoff, 2010; Wong et al., 2007), while consolidation is facilitated (Barsegyan et al., 2010) depending, however, on the brain state, e.g., sleep *vs* wake (Wilhelm, Wagner, & Born, 2011); *the type of coupling between timing* (recall test) *and dosage* (levels of cortisol and their relationship to the inversed U-shaped dose–response curve) is a key factor underlying dual effects (Sandi, 2011); *the type of experimental design/memory construct* such as brief/mild learning experience (Baker & Kim, 2002; Diamond, Campbell, Park, Halonen, & Zoladz, 2007) *vs* strong and/or extensive training (de Quervain et al., 1998; Sandi & Pinelo-Nava, 2007) and free/cued recall *vs* recognition tests may bring about differential effects; *the nature of the cognitive challenge* – through the characteristics of its associated neurocircuit recruitment – is a key determinant of vulnerability and sensitivity to interference because of the different degrees of difficulty involved (Haberlandt, 1999) and probably a different localization in neural structures (Brown & Aggleton, 2001; Buckner & Wheeler, 2001; Rugg & Yonelinas, 2003) with cognitive processes involving short (as frequently is the case for free recall tests) and/or mild challenges being particularly susceptible to disruption. Recognition memory tasks as the one used in the current experiment are typically considered episodic memory tasks, as they involve the formation and retrieval of a memory trace specific to the single study episode (therefore with specific temporal and contextual features). Deep and shallow encoding may affect recollection (involving the recovery of contextual details) and familiarity (without the retrieval of any contextual information) to a different degree (Gardiner & Richardson, 2000).

The total number of words presented at the retrieval phase was the same as that used for the encoding phase so that the retrieval task could be performed within the time-window for the cortisol non-genomic effects, i.e. about 15 min. Forty words (20 from the deep, and 20 from the shallow encoding blocks) were selected from the eighty words administered at the encoding phase and presented again (test items) intermixed with 40 new words (distractors) in a single retrieval block test. Given that all old words from the different deep and shallow encoding tests were presented and mixed together in the same block during the retrieval memory test, the same single false alarm rate holds across all conditions (Kohler et al., 2004).

Subjects were requested to say whether they had seen the word in the encoding phase ('old') or not ('new'). They were asked to press the left button of the mouse if they recognised the word as old, and the right button of the mouse if they recognised the word as new.

In both the encoding and retrieval phase, stimuli were presented for 500 ms with an inter-trial interval of 5000 ms, during which the black background was continuously presented on the screen. Brief practice sessions preceded the experiment.

In the ten subjects (five of whom received the i.v. administration at encoding, while the remaining five received the i.v. administration at retrieval) who agreed with the blood extraction procedure, cortisol plasma level was monitored by taking a blood sample through an indwelling catheter positioned in the left forearm before, 5 min after the injection of cortisol or saline, i.e. just before the beginning of the task, and at the end of the encoding or retrieval task (i.e. 15 min from task onset), depending on the randomisation list.

2.3. Statistical analyses

The primary interest was to assess whether memory retrieval was affected by cortisol administration and, if so, whether this effect emerged if cortisol was administered prior to encoding or retrieval. We therefore conducted two separate ANOVAs for administration at encoding and at retrieval, each contrasting the placebo and the cortisol groups. The accuracy of recognition judgments was established with the discrimination index P_r (the proportion of hits minus the proportion of false alarms) (Snodgrass & Corwin, 1988). The ANOVAs were run on accuracy of recognition judgements and Reaction Times (RTs), and included level of processing as within-subjects factor (deep or shallow encoding), and group as between-subjects factor (cortisol, placebo).

3. Results

Fig. 1 shows cortisol plasma level before, 5 min and 20 min after cortisol or saline injection. Five minute after the cortisol administration, the mean cortisol plasmatic concentration was 400 ng/ml. The injection of saline solution performance did not increase cortisol levels when compared with baseline levels.

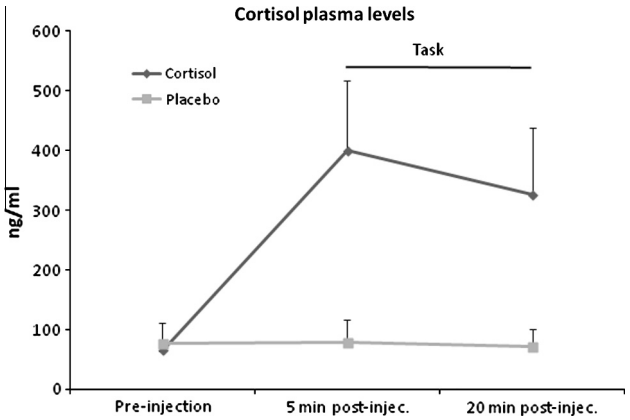

Fig. 1. Mean (SD) cortisol plasma levels before, 5 min after the intravenous bolus of 20 mg cortisol or 0,2 ml saline solution and at the end of the task (20 min after the injection) in ten subjects (five of whom received the i.v. administration at encoding, while the remaining five received the i.v. administration at retrieval).

Table 1
Proportion of responses in the recognition memory task and response times (ms in italics) for hits.

	Administration prior to encoding and response times		Administration prior to retrieval and response times	
	Cortisol	Placebo	Cortisol	Placebo
Hits deep	0.69 (0.15) *1082 (272)*	0.62 (0.14) *821 (189)*	0.63 (0.15) *1195 (224)*	0.53 (0.22) *818 (188)*
Hits shallow	0.60 (0.07) *1125 (293)*	0.53 (0.11) *869 (193)*	0.44 (0.16) *1300 (230)*	0.50 (0.13) *836 (214)*
False alarms	0.31 (0.06)	0.30 (0.12)	0.22 (0.12)	0.33 (0.15)

Standard deviations are displayed in brackets.

Table 1 reports the proportion of responses in the recognition memory task. When administration, irrespective whether cortisol or placebo, occurred prior to encoding, a significant main effect of level of processing emerged ($F_{1,14} = 7.75$, $P = 0.015$, partial $\eta^2 = 0.356$), indicating that accuracy was higher for words encoded with the deep encoding task (discrimination index $P_r = 0.348$ for deep and 0.262 for shallow encoding). No main effect ($P = 0.406$) or interaction involving group ($P = 0.905$) emerged.

When cortisol administration occurred prior to retrieval, a main effect of group emerged ($F_{1,14} = 6.05$, $P = 0.028$, partial $\eta^2 = 0.302$). Recognition accuracy was on the whole higher for individuals who received cortisol ($P_r = 0.319$) compared to placebo ($P_r = 0.189$). The interaction between level of processing and group ($F_{1,14} = 6.67$, $P = 0.022$, partial $\eta^2 = 0.323$) was also significant. As evident from Fig. 2, the higher discrimination accuracy for the cortisol group was significant for words encoded with the deep (independent samples t-test, $t_{14} = 2.88$, $P = 0.012$, $P_r = 0.412$), but not with the shallow ($P = 0.259$, $P_r = 0.224$), encoding task. In addition, similarly to administration prior to encoding, the main effect of level of processing ($F_{1,14} = 14.28$, $P = 0.002$, partial $\eta^2 = 0.505$) showed that recognition accuracy was on the whole higher for words encoded in the deep encoding task ($P_r = 0.309$ for deep and 0.198 for shallow encoding). When we directly confronted the administration before encoding and retrieval in the same ANOVA with factors of group (cortisol/encoding, placebo/encoding, cortisol/retrieval, placebo/retrieval) and level of processing (deep, shallow), the main effect of group and the interaction between group and level of processing was not significant (p 0.094 and 0.100, respectively).

In addition, Table 1 reports Reaction Times (RTs) for the cortisol and placebo groups, separately for administration prior to encoding and retrieval. In both cases, significant main effects of group emerged (administration prior to encoding, $F_{1,14} = 4.81$, $P = 0.046$, partial $\eta^2 = 0.256$; administration prior to retrieval, $F_{1,14} = 17.23$, $P = 0.001$, partial $\eta^2 = 0.552$). As evident from Fig. 3, the time taken to make correct recognition judgments was on the whole slower for individuals who received cortisol, irrespective of the level of processing at encoding.

4. Discussion

The main result of this study is that an intravenous administration of cortisol immediately preceding (5 min) the retrieval phase significantly enhanced episodic memory for neutral words. This effect was mainly driven by an increased recognition accuracy for words encoded through deep semantic operations, rather than by words encoded through shallow phonological processes.

Our findings substantiate the model proposed by Sandi (2011) whereby facilitating effects on memory processes are observed when moderate-to-high glucocorticoids elevations converge in time with the neural activity engaged by the cognitive challenge. Under our experimental conditions, memory retrieval was facilitated by plasma cortisol elevation induced by exogenous administration that took place shortly before the memory task. We used a 20 mg dose of cortisol which increased plasma cortisol baseline levels to a mean peak value of 400 ng/ml 5 min after the intravenous injection. A rise in peripheral cortisol levels, reaching moderate-to-high glucocorticoids elevations, produces a rapid increase in cortisol levels in the hippocampus in parallel with a specific increase in presynaptic glutamate release (Venero & Borrell, 1999). This is capable of affecting excitatory transmission immediately in brain regions other than the hippocampus, such as the motor cortex in humans (Milani et al., 2010). One recent study in humans (Schilling et al., 2013), in which the effects of different doses of intravenous cortisol on memory were compared following a non-genomic timescale, tested for the presence of an inverted U-shaped dose response curve, as observed in behavioural and elec-

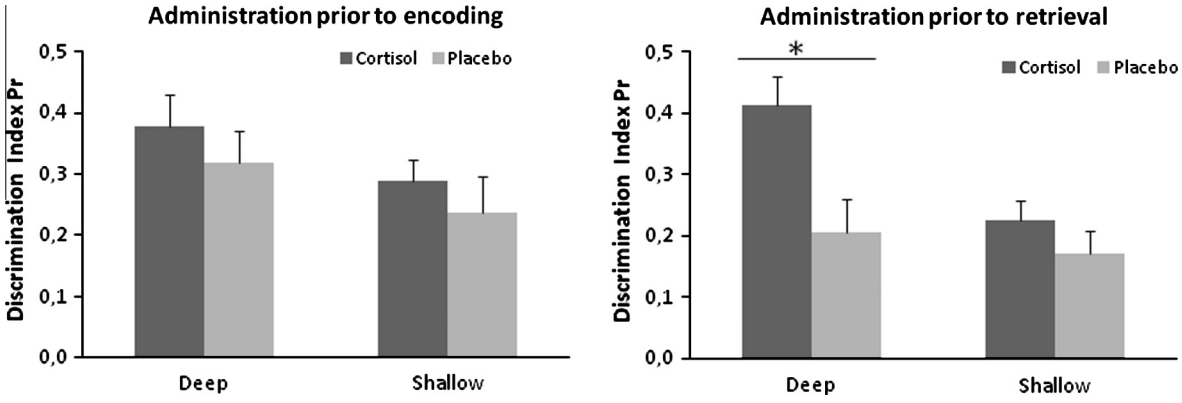

Fig. 2. Recognition accuracy (mean, SE) for administration prior to encoding (left) and retrieval (right), for individuals who received cortisol and saline solution. When cortisol administration occurred prior to encoding, no significant effect or interaction involving group emerged. Recognition accuracy was significantly different for deeply-encoded words in participants who received cortisol on retrieval with respect to placebo group.

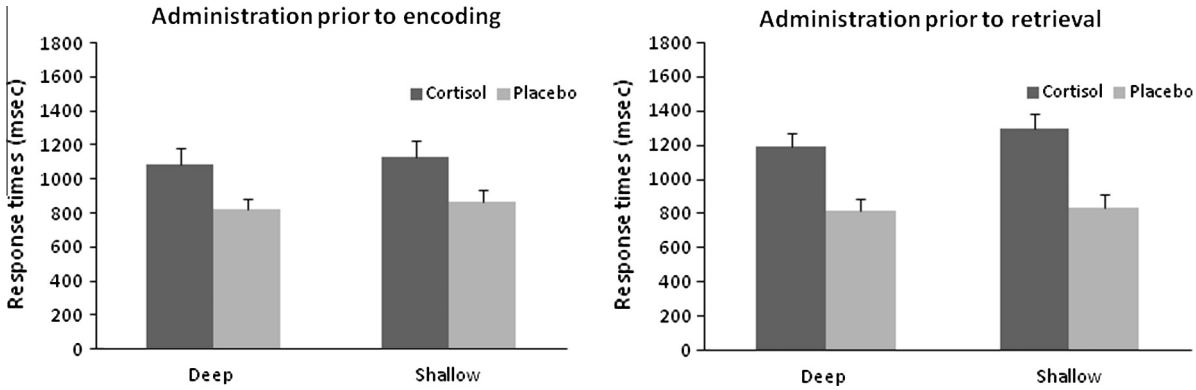

Fig. 3. Response times for administration prior to encoding (left) and retrieval (retrieval), for participants who received cortisol and saline solution. Response times were higher in participants who received cortisol, irrespective of the memory phase.

trophysiological animal studies (see Lupien & McEwen, 1997 for review; Sapolsky, 2003). Judging from the dose–response relationship between salivary cortisol levels and recall performance obtained in the aforementioned study, the cortisol levels elicited in our study may correspond to the descending limb of the inverted U-shaped dose–response curve. If so, it is possible that the effects of cortisol on memory retrieval may have been underestimated in our case, given that moderate elevation of salivary cortisol resulted in the best recall performance. However, circulating corticosteroid levels *per se* are not always informative about the local effectiveness of the hormone (Joels, 2006). Indeed, local steroid-metabolizing enzyme activity could lead to concentrations that deviate substantially from plasma hormone concentrations (Seckl & Walker, 2004). In addition, brain regional differences in local enzymatic activity or of transport molecules could further contribute to differences in hormone dose-dependent effects.

With respect to the large but somewhat confusing body of literature (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; de Quervain et al., 1998, 2003; Domes, Rothfischer, Reichwald, & Hautzinger, 2005; Kuhlmann, Kirschbaum, & Wolf, 2005), the novelty of our methodological approach in humans has been to incorporate the principles of the convergence in time and space model by coupling cortisol peak elevation (time) with the cognitive task and the characteristics of its associated neurocircuit recruitment (space). We previously demonstrated that is possible to induce facilitatory effects in frontal cortical activity – in terms of increased cortical excitability – 5 min after the intravenous injection of cortisol in humans (Milani et al., 2010). Because of such a short latency from the administration, these effects are likely compatible with a non-genomic mechanism mediated through physiochemical interactions with cellular membranes, membrane-bound receptors, and cytosolic receptors. Indeed, membrane-bound glucocorticoid receptors that are coupled to G-protein-coupled receptors have been implicated in the fast-inducing actions of corticosterone in prefrontal cortex-dependent cognition (Barsegyan et al., 2010). Recent findings in rodents show that non-genomic corticosterone effects on memory retrieval are most likely mediated via MRs located at the extracellular side of neuronal cell membranes by an increase in the frequency of miniature excitatory postsynaptic currents (Dorey et al., 2011; Pasricha, Joels, & Karst, 2011). Thus, one important difference between our findings and previous literature may lie in the time elapsing between cortisol administration and the memory test. In most human studies, memory performance impairments were noted when cortisol had been orally administered several minutes before retrieval (de Quervain et al., 2000, 2003; Domes et al., 2005; Kuhlmann et al., 2005). It has been suggested that the oral administration cannot be ascribed to a non-genomic, rapid effect (Groeneweg, Karst, de Kloet, & Joels, 2011). In addition, cortisol may exert differential effects according to the mnemonic operation involved in the test. Detrimental effects on episodic retrieval were found when memory was probed with free recall (de Quervain et al., 2003; de Quervain et al., 2000; Kuhlmann et al., 2005) but not with recognition, as in the present study. Recall involves an active search for items in memory and benefits from strategic, goal-directed operations in addition to declarative memory (Moscovitch, 1992). Cortisol may thus impair goal-directed processes (Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012) involved in recalling information from memory, while leaving other declarative operations that contribute to recognition performance unaffected, if not enhanced. A key determinant of our study was the level-of-processing approach which entailed two memorization strategies (semantic or deep, perceptual or shallow). Using this approach we could show that cortisol administered prior to retrieval specifically enhanced recognition accuracy of words encoded with the semantic judgment task. This raises the intriguing possibility that cortisol enhances recall memory for items with deeper memory traces, i.e., increased successful retrieval depends on the degree of overlap between the type of cognitive processing engaged by retrieval cues (semantic/associative) and the type of cognitive processing engaged earlier during encoding. Neuroimaging evidence shows that brain functional connectivity differs according to the level of processing with an increase between the left hippocampus and bilateral ventrolateral prefrontal cortex and right temporoparietal junction during deep processing (Schott et al., 2013). Thus, the recruitment of this particular network through deep cognitive operations occurring shortly after the enhancement of plasma cortisol levels may actually underlie the operational "space" and "time" principles of the model.

Cortisol administration before encoding did not affect the subsequent retrieval performance (either for deep or shallow stimuli), despite a trend for a facilitating effect, as shown in Fig. 2. Previous studies on the effects of cortisol administered prior to encoding yielded conflicting results. Investigations reported enhancing (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Buchanan & Lovallo, 2001), detrimental (Tops et al., 2003) or no effects (de Quervain et al., 2000). In general, pre-encoding cortisol effects are more pronounced for emotional-arousing tasks (Abercrombie et al., 2003; Buchanan & Lovallo, 2001; Kuhlmann & Wolf, 2006a, 2006b). These tasks involve noradrenergic activation, which plays a crucial role in modulating declarative memory (Maheu, Joober, Beaulieu, & Lupien, 2004). Episodic encoding is affected by interactions between glucocorticoids and noradrenalin in the amygdala (van Stegeren, Roozendaal, Kindt, Wolf, & Joels, 2010), which in turn mediates brain activity in the prefrontal cortex (Roozendaal et al., 2009). Pharmacological cortisol administration does not lead to an enhanced release of noradrenaline,

especially when the investigation does not involve emotionally arousing material as in the present study.

RTs in the present study were significantly slower after cortisol injection, irrespective of depth of encoding and memory phase of administration. This contrasts with previous investigations that showed a decrease of the time taken to give correct memory judgments after cortisol administration (McAllister-Williams & Rugg, 2002). Our results are instead more in line with the working memory literature that commonly reports an increase in response times (Lupien, Gillin, & Hauger, 1999; Oei, Everaerd, Elzinga, van, & Bermond, 2006; Schoofs, Preuss, & Wolf, 2008). It should be noted, however, that most studies that investigated the effects of cortisol on episodic memory probed memory with recall. Response times are usually not recorded with this type of memory test, and even when the study included a recognition test, response times were not reported (Abercrombie, Wirth, & Hoks, 2012; Abercrombie et al., 2003; de Quervain et al., 2000, 2003; Koessler, Steidle, Engler, & Kissler, 2013; Kuhlmann et al., 2005). It is thus difficult to interpret our result on the basis of previous findings alone. One explanation is that cortisol elevation made the set of processes that give rise to recognition judgments on the whole slower. Alternatively, the action of cortisol targeted specific aspects of the process. For instance, participants in the cortisol groups were less confident in their responses and/or judged the previous occurrence of the item through slower, recollection-based processes as opposed to rapid, familiarity-based decisions.

Several limitations need to be addressed. The intravenous manipulation itself may have increased subjects' arousal level. The sample size was small and the group of subjects was restricted to a male sample. Sex differences in cortisol effects on memory (Abercrombie et al., 2012; Stark et al., 2006) and, in general, in the relationship between memory and stress (Wolf, 2009) exist. Thus, our results for male subjects are not necessarily representative for females for whom the stress response may be modulated by the menstrual cycle and hormonal contraception. The relative contribution of familiarity and recollection to the observed effects of cortisol was not investigated, as our experimental paradigm did not involve a separate measure of the two processes (e.g., remember and know responses).

In conclusion, our study demonstrated that cortisol determines an enhancement in episodic memory if administered immediately prior to retrieval, and this effect is more evident if the memory trace is laid down through deep encoding operations. Cortisol administration prior to encoding only produced negligible enhancing effect. Future studies will need to assess which specific memory processes are affected by cortisol by directly comparing more tasks, and different recognition memory components.

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