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## **EFFECTS OF CORTISOL ON THE LATERALITY OF THE NEURAL CORRELATES OF EPISODIC MEMORY**

**Hamid A. Alhaj; Anna E. Massey and R. Hamish McAllister-Williams** ✉

*Psychobiology Research Group, **Institute of Neuroscience**, Newcastle University,  
Newcastle upon Tyne, United Kingdom*

### **Correspondence should be addressed to:**

Dr Hamish McAllister-Williams,

Psychiatry, Leazes Wing,

Royal Victoria Infirmary,

Newcastle upon Tyne, NE1 4LP,

United Kingdom

Tel: +44 (0)191 282 4034

Fax: +44 (0)191 222 6162

Email: [r.h.mcallister-williams@ncl.ac.uk](mailto:r.h.mcallister-williams@ncl.ac.uk)

## **Abstract**

Alterations in the laterality of cortical activity have been shown in depressive illnesses. One possible pathophysiological mechanism for this is an effect of corticosteroids. We have previously demonstrated that endogenous cortisol concentrations correlate with the asymmetry of cortical activity related to episodic memory in healthy subjects and depressed patients. To further-examine whether this is due to a causal effect of cortisol on the laterality of episodic memory, we studied the effect of exogenous administration of cortisol in healthy subjects. Twenty-three right-handed healthy male volunteers were tested in a double-blind cross-over study. Event-related potentials (ERPs) were recorded during an episodic memory task following a four-day course of 160 mg/day cortisol or placebo. Low-resolution brain electromagnetic tomography (LORETA) was used to identify brain regions involved in the neurocognitive task. Cortisol levels were measured in saliva samples. ERP and LORETA analysis following placebo demonstrated significant left parahippocampal activation associated with successful retrieval. Cortisol led to a decrease in the mean early frontal ERP voltage and an increase in the late right ERP voltage. LORETA suggested this to be due to a significant increased late activation of the right superior frontal gyrus. There was no significant effect of cortisol on episodic memory performance. This study suggests that exogenous cortisol leads to more positive-going waveforms over the right than the left hemisphere, possibly due to increased monitoring of the products of retrieval. The results support the hypothesis of causal effects of cortisol on the laterality of cortical activity occurring during an episodic memory task.

**Keywords:** Cortisol; Episodic Memory; Asymmetry; Stress, electroencephalography (EEG); Event-Related Potentials (ERPs).

## Introduction

Corticosteroids (cortisol in man and corticosterone in rodents) act on the brain inducing alterations in mood, emotion and neurocognitive functions. Many studies have investigated the effects of cortisol administration in healthy humans on episodic memory, memory for previously encountered events, with some demonstrating impaired memory (Newcomer et al., 1999; McAllister-Williams and Rugg, 2002).

Episodic memory has also been shown to be impaired in patients with depression, a disorder that is frequently associated with increased cortisol concentration. Therefore, studies of the effects of cortisol on episodic memory are essential in full understanding the underlying mechanisms involved in the pathology associated with depressive illness. The effects of corticosteroids on neurocognitive processes have been demonstrated to be dose- and time-dependent (Lupien and McEwen, 1997). In rodents, hippocampal long-term potentiation (LTP), which may be a neurobiological correlate of memory, has been shown to have an inverted-U shape correlation with corticosteroids (Diamond et al., 1992). Similarly, some human studies have also indicated inverted-U shape correlation between exogenous cortisol dose and memory performance. Lupien and colleagues found that while a high dose of cortisol impaired working memory, a low dose actually improved memory performance (Lupien et al., 1999).

Cortical activity, as assessed using EEG and fMRI methodology, in general shows asymmetry during the performance of cognitive task, with this presumably reflecting the cerebral localisation of cortical networks involved in cognition. Changes in asymmetry occur in states of emotional disturbance, such as stress, anxiety and

**depression.** Relative greater right frontal activity, demonstrated by less frontal alpha electroencephalography (EEG) frequency, has been found in fearful and distressed children (Calkins et al., 1996; Fox, 1994; Schmidt and Fox, 1998) and anxious and depressed adults (Coan and Allen, 2004; Allen et al., 2004; Davidson, 1998; Henriques and Davidson, 1991). Corticosteroids may play a part in the EEG asymmetry seen in stressful conditions. Indeed, it has been shown that 4 days of administration of 160 mg of the synthetic glucocorticoid prednisone to healthy subjects alters the laterality of alpha EEG, increasing right frontal activation (Schmidt et al., 1999). Similar findings have also been shown following acute treatment with cortisol in healthy subjects (Tops et al., 2005).

Asymmetry in the electrophysiological correlates underlying episodic memory has been shown in healthy humans (Tulving et al., 1994; Baddeley, 2001). Asymmetrical frontal and prefrontal cortex (PFC) activity, with relatively higher right hemisphere activity, has been reported in many (Tulving et al., 1994; Ragland et al., 2000; Bernard et al., 2001) but not all studies of episodic retrieval (Cabeza and Nyberg, 2000; Mayes A R and Montaldi D, 2001). Event-related potential (ERP) data have shown differences in waveforms associated with accurate memory recollection when subjects are presented with a previously studied item compared to correct identification of new non-studied items (Wilding and Rugg, 1997; McAllister-Williams and Rugg, 2002; Alhaj et al., 2006). This “old/new” effect comprises two components: a left parietal activity, which is believed to reflect hippocampal-modulated cortical activation underlying episodic memory retrieval (Alvarez and Squire, 1994; McClelland et al., 1995) and right frontal activity, which is believed to originate

from PFC and may reflect evaluation and monitoring processes that operate upon the products of memory retrieval (Rugg et al., 2002;Rugg et al., 1996).

We have previously shown that endogenous cortisol concentrations correlate with the laterality specific to episodic memory retrieval in depressed patients and healthy subjects (Alhaj et al., 2007). In particular, cortisol concentrations were demonstrated to correlate negatively with the early left parietal and positively with the late right frontal ERP “old/new” effect components (Alhaj et al., 2007). We hypothesise that the correlation between endogenous cortisol and cortical asymmetric activity is due to a causal effect of cortisol. To test this hypothesis, we utilised a four-day exogenous cortisol administration paradigm in healthy subject who underwent an episodic memory task. The neural correlates of retrieval were assessed using ERPs and low-resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994;Pascual-Marqui et al., 1999).

## **Subjects and Methods**

### **Subjects**

Twenty-three healthy male subjects aged between eighteen and thirty-three were recruited by advertisement from the local population. Subjects were compensated for their time and expenses. They were provided with information sheets and written informed consent was obtained. Ethical approval was granted by the Local Research Ethics Committee. Cerebral dominance was assessed using Briggs’ modification of Annett’s (Annett, 1967) handedness inventory (Briggs and Nebes, 1975) and only right-handed individuals were recruited.

The inclusion criteria required that all subjects had an IQ of ninety or more as assessed by the National Adult Reading Test (NART) to ensure that they comprehended the task instructions. It was also required that their first language was English in order to be familiar with all the words used in the experiment. All the subjects were healthy and not taking any medication. Females were not included in this study due to the potential interactions of the menstrual cycle with the HPA axis and because of ethical difficulties related to pregnancy checking and oral contraceptive pill interactions with the HPA axis. Subjects were excluded if there was evidence of past or present history of significant medical or psychiatric disorders (including drug and alcohol misuse) or if they had a first-degree relative with a history of a psychiatric disorder. This was ensured by a structured personal and family history administered by a research doctor. Subjects' mood was assessed using the Hamilton Depression Rating Scale (HDRS) –21 items, Beck Depression Inventory (BDI) and Profile of Mood State (POMS). In this study, subjects were excluded if they scored 8 or more on HDRS.

## **Design**

A double-blind, placebo-controlled, crossover design was used. Subjects were tested on two occasions following a four-day course of either cortisol (160 mg of hydrocortisone P.O. daily) or placebo in a random-balanced order. The cortisol was taken as 100 mg at 8:00 a.m. and 60 mg at 8:00 p.m. to mimic the circadian rhythm of endogenous cortisol secretion. The first dose was taken in the evening of day 1. A minimum of a two-week interval between treatments was used to minimise any carry-

over effects of cortisol. The cortisol administration paradigm, previously used by Newcomer et al (1999), was proposed to increase levels of cortisol to those found after severe stress. The subjects were asked to record the time they took the medication and the duration and quality of sleep (using a 100 mm. analogue scale) in a logbook. Subjects were issued with a Steroid Treatment card and a 24-hour contact number for a research doctor in the event of concern or emergency. Memory tests and EEG recordings were performed in the afternoon (approximately 13:30- 14:30 h.) of day 5, subjects having taken their last dose of medication at 08:00 h. that day.

### **Cortisol Assay**

Four saliva samples were collected from the subjects on each visit at 12:30, 13:30, 14:30, and 15:10 h. using saliva collection tubes (“Salivettes”, Sarstedt, Germany). Salivary measurement of cortisol offers a non-invasive method that provides reliable estimates of circulating cortisol levels (Goodyer et al., 1996). Cortisol in saliva represents the biologically active (unbound) hormone fraction and it is independent of salivary flow rate. The assays of cortisol levels in the saliva samples were performed by means of radio-immunoassay (RIA) using Gamma-B <sup>125</sup>I corticosteroid RIA kits obtained from Immuno-diagnostic Systems Limited (Tyne & Wear, UK). Intra- and inter-assay variations for salivary cortisol were 5.1% and 4.2%, respectively.

### **Episodic Memory Task**

The techniques employed were identical to those employed in previous studies (McAllister-Williams et al., 2002;Alhaj et al., 2006). In brief, stimuli consisted of low frequency words selected from the corpus (Kucera and Francis, 1967). In the

study phase subjects were presented with two lists of word presented binaurally. In each word list, half of the words were spoken in a male voice and half in a female voice randomly determined. Associated test lists were created with 50% old words presented in the study lists and 50% new words. Test lists of words were presented visually on a computer monitor, with each word presented for 500 ms and subtending a vertical angle of 0.5° and a maximum horizontal angle of 2.8°. Subjects were exposed to two different study/test lists on each of the two recording sessions. On each of two visits subjects underwent an orientation and preliminary practice session utilising study and test words not included in the actual experiment. Following the practice, subjects undertook two study/test cycles, as described above.

As in previous investigations (Wilding and Rugg, 1996;McAllister-Williams and Rugg, 2002), the voice in which each study item was presented dictated which of two tasks should be performed. Subjects were instructed to listen to each word and to respond verbally by repeating the word aloud and then judge whether it was active/passive or pleasant/unpleasant. This procedure was followed to enhance encoding of study words and the context in which they appeared. The study phase was followed by a period of 5 minutes rest, during which the subject's attention was distracted **by asking them to read through a magazine**, and then the test phase was conducted. First, an asterisk appeared on a computer screen as a fixation point and to advise the subject that they were about to see the stimulus word. Then a word was presented and the subject was asked to respond as quickly and accurately as possible to whether this was an old (studied) word they had heard during the study phase or a new (unstudied) one, using the thumb of either their left or right hand. A question mark appeared on the screen following the subject's response as a prompt to the



subject that they should indicate the gender of the voice that spoke the word in the study phase by pressing one of the two buttons. No response was required if the word was new. For each subject, the same evaluation of the voice (pleasant/unpleasant or active/passive) and the same button assignment (old/new, male/female) remained consistent in both visits to avoid any possible confusion. These voice and button assignments were counterbalanced across subjects. The total time including orientation/practice study-test block and two experimental study-test blocks was approximately 70 min.

### **EEG Recordings**

EEG was recorded using an elasticated cap (Easy Caps, Germany) with 29 silver/silver chloride electrodes placed on the scalp in accordance with the International 10-20 system (American Electroencephalographic Society, 1994). Two additional electrodes were placed on the mastoid processes, with the left mastoid acting as a reference to all scalp EEG channels. The EEG was algebraically reconstructed off-line to represent recordings with respect to an average mastoid reference. Vertical electrooculography (VEOG) was recorded between electrodes placed below each eye and an electrode placed on the nasion. Horizontal EOG (HEOG) was recorded between electrodes placed on the outer canthus of the left and right eyes. EEG and EOG were filtered with a bandpass of 0.01-30 Hz and sampled at a rate of 6 ms per point.

## **EEG Analysis**

Prior to epoching, EEG data underwent a basic analysis procedure using Neuroscan analysis software (Scan 4.1, NeuroSoft Inc., USA). Sections of data that contained gross artefacts (e.g. movement and scalp muscle contraction) were manually removed. Both blink-correction, employing the data recorded in the VEOG channel and using the algorithm developed by (Semlitsch et al., 1986), and correction of electrocardiographic (ECG) artefacts, using principle component analysis, were conducted using the Neuroscan software. The EEG was then epoched into 1536 ms segments beginning 102 ms before the onset of words presented in the test phase. Any epoch containing residual artefact was rejected if any channel, except VEOG, had a voltage deflection greater than  $\pm 75\mu\text{V}$ . Average ERPs were generated for each subject for recognised old words attracting correct source judgements (“hit-hits”: HH), and for correctly identified new items (“correct rejections”: CR). To maintain an acceptable signal/noise ratio, a lower limit of 20 artefact-free epochs per subject per visit per response category was set.

## **Source Localisation of the Electric Activity**

LORETA was used to estimate the three-dimensional intracerebral current density distribution from the scalp electric potential differences (Pascual-Marqui et al., 1994; Pascual-Marqui et al., 1999). In this method, the cortical grey matter is modelled as 2394 voxels using the digitized Talairach atlas (Talairach J and Tournoux P, 1988), with each voxel occupying a volume of  $0.343\text{ cm}^3$  (Pascual-Marqui et al., 1999). LORETA depends on a “smoothness assumption” according to which neighbouring neuronal populations are assumed to show highly correlated activity,

thus solving the non-unique ‘inverse’ problem that results from the calculation of the electric sources from potentials recorded on the scalp surface (Pascual-Marqui et al., 1999). The resulting solution has relatively low spatial resolution, preserving the location of maximal activation with some dispersion. Accumulating literature has shown LORETA localisation to be consistent with functional magnetic resonance imaging (fMRI) results (Seeck et al., 1998). Indeed, recent results from our lab have shown that LORETA statistical software successfully identified the neural generators of episodic memory retrieval to be the hippocampus (Alhaj et al., 2006). However, some other simulation studies have questioned LORETA’s ability to localise small and deep generators, such as the hippocampus (Menendez and Andino, 2000;Phillips et al., 2002;Fontanarosa et al., 2004). Bearing this in mind, the results of LORETA in this study were used to supplement analysis of the scalp localisation of electrical activity.

### **Statistical Analysis**

All values are quoted as means  $\pm$  standard deviations. Statistical comparisons were made using analysis of variance (ANOVA) incorporating the Geisser-Greenhouse correction for inhomogeneity of covariance. F ratios are reported with corrected degrees of freedom. Statistical significance was adjudged at the  $p < 0.05$  level. LORETA software (LORETA-KEY version June 2003; The Key Institute for Brain–Mind Research, Switzerland) was used to perform statistical non-parametric mapping (Pascual-Marqui et al., 1994;Pascual-Marqui et al., 1999) and identification of underlying neural generators of ERPs associated with different conditions during the episodic memory test. Statistical non-parametric paired t-tests were performed for the

comparison of current density distribution between conditions on a voxel-by-voxel basis, corrected for multiple testing (Thomas and Holmes, 2002).

## **Results**

### **Subjects**

Subjects' mean age was  $21.2 \pm 3.2$  years (range 18-33) and their IQ was  $108.6 \pm 7.5$  (range 92-122). Subjects were confirmed as euthymic with a baseline BDI of  $1.3 \pm 2.0$  (range 0-8) and HDRS of  $0.3 \pm 0.7$  (range 0-3). Seventeen out of twenty-three subjects were non-smokers and sixteen were non-users of illicit drugs, while seven noted infrequent use of recreational drugs. Mean body mass index (BMI) for subjects was  $23.3 \pm 2.2$  (range 18.9-30). Cortisol was well tolerated and there were no significant side effects. There was no difference in either sleep duration ( $7.6 \pm 1.0$  vs.  $7.8 \pm 0.8$  hours) or subjective quality ratings ( $64.8 \pm 11.2\%$  vs.  $66.5 \pm 14.4\%$ ) between the period that cortisol and placebo were administered respectively ( $p > 0.1$ ). Mood scores, as assessed by BDI and POMS, did not differ between baseline and after taking cortisol ( $p > 0.1$ ).

### **Cortisol Concentrations**

Salivary cortisol concentrations at the start of testing were significantly higher after cortisol administration than after placebo ( $157.2 \pm 141.9$  vs.  $3.8 \pm 1.8$  nmol/l;  $t(1,20) = 5.0$ ,  $p < 0.001$ ). A slight drop in cortisol concentrations following placebo treatment was observed throughout the test period (see figure 1), which was expected due to normal diurnal rhythm. Following cortisol treatment, cortisol concentrations

decreased logarithmically over the test period (figure 1). No rise in cortisol levels was seen after episodic memory testing in both treatment phases suggesting that testing was not by itself stressful enough to lead to significant cortisol release.

**Fig 1 near here**

### **Episodic Memory Performance**

Behavioural analysis was carried out on data collapsed across gender of voice speaking the items at study, since no effect of gender was found in previous identical studies (Wilding and Rugg 1996, McAllister-Williams and Rugg 2002). In line with these studies, trials in which words were correctly judged new are referred to as 'correct rejections' (CR), and new words judged to be old as 'false alarms' (FA). Trials on which words were correctly judged to be 'old' are referred to as 'hits' (H), and if correctly assigned to their study context as 'hit/hits' (HH). Analysis of the behavioural data focused on two measures: recognition, as assessed by the discrimination index ( $pH - pFA$ ) (Snodgrass and Corwin, 1988), and recollection, as indicated by the probability of correct study context judgement given recognition ( $pHH/pH$ ).

ANOVA employed a within subject factor of drug (cortisol vs. placebo) and a between-subject factor of the visit the drug was administered (first vs. second). There was no significant difference between response times (RTs) for the initial item memory response, for either CR ( $1.31 \pm 0.34$  vs.  $1.26 \pm 0.28$  s;  $p > 0.1$ ) or HH responses ( $1.32 \pm 0.31$  vs.  $1.27 \pm 0.23$  s;  $p > 0.1$ ) following cortisol and placebo,

respectively. ANOVA results revealed a significant effect of visit on recognition and recollection, indicating that subjects performed better on the second visit due to a possible learning effect ( $F(1,21) = 4.4$ ;  $p < 0.05$ ). However, there was no significant effect of cortisol treatment on either recognition (placebo:  $0.72 \pm 0.10$  vs. cortisol:  $0.71 \pm 0.13$ ;  $p > 0.1$ ) or recollection (placebo:  $0.83 \pm 0.08$  vs. cortisol:  $0.82 \pm 0.09$ ;  $p > 0.1$ ).

### **ERP Analysis**

As in previous studies (McAllister-Williams et al 2002; Alhaj et al. 2006), only ERPs associated with CR and HH responses were analysed. Grand averages of the ERPs associated with HH and CR response categories from the 23 subjects following treatment with placebo are illustrated in figure (2A) while figure (2B) illustrates ERPs recorded after cortisol. The ERPs shown in both figures show the well-documented “old/new” memory retrieval effect. This effect starts from around 500 ms post stimulus with ERPs associated with HH responses being more positive going than ERPs associated with CR responses. The difference is seen to be greater over the left than the right temporo-parietal regions.

### **Figure 2 near here**

On the basis of previous published data (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002; Alhaj et al. 2006), *a priori* it was decided to analyse the mean amplitudes of four consecutive latency regions 200-500, 500-800, 800-1100 and 1100-1400 ms post stimulus, with respect to the mean of the pre-stimulus baseline.

For each latency region, repeated measures ANOVA were conducted on ERP data recorded from four clusters of three electrodes in the left anterior (FP1, F7 and F3), right anterior (FP2, F8 and F4), left posterior (O1, P7 and P3) and right posterior (O2, P8 and P4) quadrants. These clusters were again chosen *a priori* on the basis of previous data demonstrating the old/new episodic memory effect (Wilding and Rugg, 1996;McAllister-Williams and Rugg, 2002). Analysis of the clusters employed within-subject factors of response type (HH vs. CR), hemisphere (left vs. right) and location (anterior vs. posterior).

**Figure 3 near here**

As can be seen from figure 2, figure 3 and table 1, there was a significant effect of response type between 500-800 ms post stimulus, reflecting the neural activity of episodic memory retrieval as expected on the basis of the published literature (Wilding and Rugg, 1996;McAllister-Williams and Rugg, 2002). Further, significant response by anterior/ posterior (AP) interaction and response by hemisphere were found, reflecting the topography of the “old/new” effect activity previously described.

Cortisol treatment had a significant effect on ERP amplitude between 200-500 ms post stimulus, leading to **increased negativity** in ERP associated with both HH and CR. A significant drug by location (anterior vs. posterior) interaction between 200-500 and 500-800 ms post stimulus was also found due to cortisol causing more negative-going waveform frontally. There was also a significant drug by hemisphere (right vs. left) interaction in the latency regions 800-1100 and 1100-1400 due to

cortisol causing a more positive-going waveform in the right hemisphere. There was no significant drug by response by site interaction, indicating that these general effects of cortisol were irrespective of type of response and so not dependant on memory retrieval.

**Table 1 near here**

### **LORETA Analysis**

LORETA software was used to compare brain regions that contribute to the electrical activity associated with each response category (CR vs HH) in the memory task. LORETA statistical comparisons were conducted between the current density values associated with CR and HH on a voxel by voxel basis for the four latency regions (200-500, 500-800, 800-1100 and 1100-1400 ms post-stimulus). Voxel-by-voxel LORETA analysis following placebo treatment demonstrated a significant difference between HH and CR responses due to activation of the left parahippocampal gyrus in association with successful recollection between 500 and 800 ms post stimulus ( $t = 3.74$ ;  $p < 0.05$ ) (see figure 4). There was no significant difference between LORETA solutions associated with HH and CR responses in the other latency periods, including in the period 200-500 ms where a significant drug by location effect was seen on ERP amplitude ( $p > 0.1$ ).

Following cortisol treatment, LORETA current density values associated with HH and CR responses found a significant difference between 800 and 1100 ms post stimulus ( $t = 4.36$ ;  $p < 0.05$ ). This was related to maximal activation in the right



superior frontal gyrus, as shown in figure 5. Other latency periods were not found to be significantly different.

**Fig 4 near here**

**Fig 5 near here**

## **Discussion**

This study investigated the effect of an exogenous high dose of cortisol on episodic memory retrieval and the laterality of its neural circuitry. Behavioural analysis showed no effect of cortisol on episodic memory accuracy or speed of performance. The most interesting and novel finding of this study is the effect of cortisol treatment on the asymmetry of the ERPs associated with HH and CR, leading to an increase in the right frontal ERP voltage. This was supported by LORETA analysis, which revealed that cortisol led to a late significant activation of the right superior frontal gyrus during the episodic recollection task.

The effects of cortisol on the asymmetry of cortical activity related to episodic memory, by causing a more positive late deflection over the right than the left hemisphere, is a distinctive finding. This effect is related to the right frontal component of the “old/new” effect and supports the hypothesis that cortisol enhances the cortical activity that may relate to the operations that directly result from episodic memory retrieval. It is well known that GC receptors reside the frontal cortex (Diorio et al., 1993) and the increased activation of this region following cortisol treatment

may be due to increasing of the post-hippocampal monitoring of memory processing. The right/left asymmetry activity resulted from cortisol administration extends previous observations of increased right frontal activation (decreased frontal alpha EEG) following administration of cortisol or a synthetic glucocorticoid prednisone in healthy subjects (Schmidt et al., 1999;Tops et al., 2005). It is also in agreement with our previous finding of significant correlation between cortisol concentration and the asymmetry of ERPs associated with episodic memory retrieval in depressed patients and healthy subjects (Alhaj et al. 2007). However, it is in contrast to non-significant effects of a one-week administration of cortisol on the ERP asymmetry (McAllister-Williams and Rugg 2002). This difference may have occurred due to the larger daily dose used in the present study (160 mg/ day) compared to the one-week cortisol administration study (40 mg/ day). However, it is also possible that the smaller number of participants (14 subjects) in the earlier study, compared to 23 subjects in the current study, was not sufficient to show such effect of cortisol on ERP asymmetry. Our results also showed that cortisol caused an early anterior/ posterior asymmetry due to a more negative-going deflection frontally but more positive posteriorly in the HH related ERPs. This finding is similar to results from the one-week administration of cortisol (McAllister-Williams and Rugg 2002).

Following placebo, LORETA revealed that between 500 and 800 ms post stimulus, episodic recollection was associated with maximal activation of the parahippocampal gyrus, an area that is well-recognised for its role in episodic memory (Scoville and Milner, 1957;Zola-Morgan and Squire, 1993;Tulving and Markowitsch, 1998;Eldridge et al., 2000;Rugg et al., 2002). This is similar to a certain extent, given the low spatial resolution of LORETA, to our previous findings of maximal activation

of the hippocampus in identical episodic memory retrieval test in the placebo condition (Alhaj et al., 2006). However following cortisol administration, there was no significant difference between 500 and 800 ms post stimulus (i.e. the expected latency region of activation of the parahippocampal gyrus in an episodic memory task). This is likely to be due to neuronal deactivation of the neural correlates of memory retrieval caused by cortisol treatment.

The current study found no effect of cortisol on episodic memory performance, despite, at the time of testing, plasma cortisol concentrations being significantly higher after administration of cortisol than placebo. There are multiple possible explanations given the complex relationship between the effects of cortisol and memory performance. For example cortisol has a differential effect on various stages of memory function potentially enhancing consolidation and impairing retrieval (Roosendaal et al., 2006). The time of administration of exogenous cortisol is also important in that morning administration, when circulating levels are relatively high, is more prone to producing impairments while afternoon administration, during the diurnal trough, can lead to enhancement (Het et al., 2005). It is believed this is due to a “U-shaped” dose response relationship between cortisol concentrations and memory performance (Domes et al., 2005). This may be mirrored by complex temporal relationships between elevated cortisol and memory (Sauro et al., 2003). The cortisol administration paradigm used in the current study was identical to that that has been previously used by Newcomer and colleagues (1999) and found to cause impairment in delayed verbal recall. However, memory tests were conducted in the Newcomer study at 4 p.m. (compared to 1:30 p.m.) and cortisol concentrations were significantly lower than those in our study. This could explain the differences, given the U-shaped

dose response curve and the differences in effect of cortisol administration across the circadian cycle (Domes et al., 2005;Het et al., 2005). Further, although repeated exposure to cortisol may lead to impairment, it is possible that the acute effect of relatively high levels of cortisol at the time of testing, as in this study, may counteract the deleterious effect of previous chronic increase in cortisol. This hypothesis is in line with a study in mice showing that while repeated administration of cortisol attenuates 5-HT<sub>1A</sub> receptor function, an additional dose of cortisol administered 2 h prior to the test prevents this attenuation of response (Man et al., 2002). Another possible explanation for the difference in findings compared to Newcomer et al (1999) may be the fact that the hippocampus is less sensitive to acute and subacute changes of cortisol levels than the frontal and prefrontal regions. It has been suggested that working memory, which is specifically related to the frontal cortex, is more sensitive than the hippocampus-dependent episodic memory to elevated cortisol levels at the time of testing (Lupien et al. 1999).

The current study used a similar test paradigm of two previous studies investigating the effects of acute (single dose of 100 mg) and repeated (7-day course of 20 mg b.d.) cortisol administration on the neural correlates of episodic memory (McAllister-Williams and Rugg, 2002;Hsu et al., 2003). The repeated cortisol administration study showed impairment in item recognition in the episodic memory task, while cortisol concentrations were not different from those following placebo treatments at the time of testing. However, acute cortisol administration did not show a significant effect on memory performance or neural correlates of episodic memory retrieval but there was a significant increase in cortisol levels at the time of testing. Taken together, the current study and previous two studies investigating the effect of cortisol

on episodic memory in healthy subjects suggest that impairment occurs following cortisol administration over a prolonged period of time, but perhaps only if the level of cortisol is low or normal at the time of testing.

In conclusion, this study shows that subacute exposure to cortisol differentially activate right frontal brain regions, leading to a more positive waveform over the right than the left hemisphere. These results support the hypothesis of a causal role of cortisol on the electrophysiological laterality of brain activity seen during an episodic memory task. Further studies utilising different cognitive and cortisol administration paradigms are warranted to further clarify the specific nature of this effect.

## Figure Legends

**Fig. 1** Salivary cortisol concentrations following cortisol (solid line) and placebo (dashed line) treatments.

**Fig. 2** Episodic memory retrieval related electrophysiological activity following placebo (A) and cortisol (B) treatments. ERP grand average waveforms associated with correct rejection (CR) and hit-hit (HH) responses from 9 representative electrode sites, laid out as if looking down on the head from above with the front of the head at the top. CR-related ERPs are shown with a solid line, whereas HH-related ERPs are shown with a dashed line. **Negativity is plotted downwards.**

**Fig. 3** Electrophysiological activity associated with HH (A) and CR (B) responses following cortisol and placebo treatments. ERPs in the cortisol condition are shown with a solid line, whereas ERPs in the placebo condition are shown with a dashed line. All other details are as explained for Fig. 2.

**Fig. 4** LORETA source localisation of episodic memory retrieval as assessed by the comparison of HH and CR responses following placebo administration. Statistical nonparametric voxel-wise testing shows that maximal activation between 500 and 800 ms post stimulus occurs in the left parahippocampal gyrus (Brodmann Area (BA) 37 in the Limbic Lobe) ( $p < 0.05$ ). L = left; R = right; A = anterior; P = posterior. Blue colour indicates decreased activation while red colour indicates increased activation.

**Fig. 5** LORETA source localisation of episodic memory retrieval as assessed by the comparison of HH and CR responses following cortisol administration. Statistical nonparametric voxel-wise testing shows that maximal activation between 800 and 1100 ms post stimulus occurs in the right superior frontal gyrus (BA 11 in the Frontal Lobe) ( $p < 0.05$ ). L = left; R = right; A = anterior; P = posterior. Blue colour indicates decreased activation while red colour indicates increased activation.

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