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Effects of DHEA Administration on Episodic Memory, Cortisol and Mood in Healthy Young Men: A Double-Blind, Placebo-Controlled Study

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Running title: DHEA, episodic memory, cortisol and mood

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Abstract

Rationale: Dehydroepiandrosterone (DHEA) has been reported to enhance cognition in rodents though there are inconsistent findings in humans. *Objectives:* The aim of this study was to investigate the effects of DHEA administration in healthy young men on episodic memory and its neural correlates utilising an event-related potential (ERP) technique. *Methods:* 24 healthy young men were treated with a 7-day course of oral DHEA (150mg b.d) or placebo in a double blind, random, crossover and balanced order design. Subjective mood and memory were measured using visual analogue scales (VASs). Cortisol concentrations were measured in saliva samples. ERPs were recorded during retrieval in an episodic memory test. Low-resolution brain electromagnetic tomography (LORETA) was used to identify brain regions involved in the cognitive task. *Results:* DHEA administration lead to a reduction in evening cortisol concentrations and improved VAS mood and memory. Recollection accuracy in the episodic memory test was significantly improved following DHEA administration. LORETA revealed significant hippocampal activation associated with successful episodic memory retrieval following placebo. DHEA modified ERPs associated with retrieval and led to a trend towards an early differential activation of the anterior cingulate cortex (ACC). *Conclusions:* DHEA treatment improved memory recollection and mood and decreased trough cortisol levels. The effect of DHEA appears to be via neuronal recruitment of the steroid sensitive ACC that may be involved in pre-hippocampal memory processing. These findings are distinctive, being the first to show such beneficial effects of DHEA on memory in healthy young men.

Keywords DHEA, Cortisol, Episodic Memory, Recognition, Mood, Event-Related Potentials (ERPs), Low-Resolution Brain Electromagnetic Tomography (LORETA).

Introduction

Dehydroepiandrosterone (DHEA) is a steroid produced in the zona reticularis of the adrenal glands and also independently in the brain (Baulieu 1997; Majewska et al. 1990). The sulphated form, DHEA-S is the most abundant steroid in plasma and cerebrospinal fluid (CSF) in humans (Wolf and Kirschbaum 1999). DHEA may be involved in the pathophysiology of the cognitive decline with age and mood disorders.

During adulthood, DHEA concentrations decrease dramatically with age so that at age 80 are they are about one fifth of those at age 20 (Orentreich et al. 1984; Gray et al. 1991). This decline has been postulated as a possible explanation of many age-related illnesses including memory impairment (Baulieu et al. 2000). Some studies in patients with Alzheimer's disease have shown a significant correlation between cognitive impairment and low plasma concentrations of DHEA-S compared with controls (Nasman et al. 1991; Yanase et al. 1996), though a number of other studies have found no such difference between patients with Alzheimer's disease and healthy controls (Leblhuber et al. 1993; Carlson et al. 1999). An inverse correlation between DHEA concentrations and cognition has been also shown in elderly females (Breuer et al. 2001). However, other studies have failed to reveal any significant correlation between DHEA and/or DHEA-S and the age-related decline in cognition (Barrett-Connor and Edelstein 1994; Moffat et al. 2000).

Administration of DHEA has been suggested as a possible neuro-protective intervention that may impede decline in memory and cognitive function in normal

ageing and dementia (Bologa et al. 1987; Nasman et al. 1991). Indeed, many rodent and other animal studies have demonstrated that DHEA administration enhances memory performance in healthy young (Flood et al. 1988; Migues et al. 2002), as well as in ageing and cognitively impaired animals (Flood and Roberts 1988; Shi et al. 2000). However, the extrapolation of such findings in animals to humans is problematic since DHEA concentrations in rodents are significantly lower than in man (Vallee et al. 2001). Further, in humans results have been inconsistent and almost all placebo-controlled trials have found no beneficial effects on memory in healthy old subjects (Barnhart et al. 1999; Wolf et al. 1997; Wolf et al. 1998; van Niekerk et al. 2001) or patients with Alzheimer's disease (Wolkowitz et al. 2003). This could be due to the use of different dosage, variation of period of DHEA administration and age of subjects.

It is well documented that the Hypothalamic Pituitary Adrenal (HPA) axis is dysfunctional in depression (McAllister-Williams et al. 1998). Abnormally high cortisol concentration is a frequent, though not consistent finding, in depressed patients (Dinan 1994; Arborelius et al. 1999). DHEA has also been implicated in the pathophysiology of depressive illness. DHEA and DHEA-S have been demonstrated to be inversely correlated with depressive mood (Barrett-Connor et al. 1999) and DHEA administration has been shown to improve mood in patients with depression (Wolkowitz et al. 1999), though there has been a report of elevated DHEA in major depression (Heuser et al. 1998). This effect could relate to DHEA acting as a functional cortisol antagonist (Browne et al. 1992; Kalimi et al. 1994), including counteracting the deleterious effects of corticosteroids on neuropsychological function in rodents (Kaminska et al. 2000). It has been argued that the functional

hypercortisolaemia seen in depression is best assessed by measuring Cortisol/DHEA ratio (Goodyer et al. 1998), which is found to be increased in cognitively impaired drug-free depressed patients compared to healthy controls (Young et al. 2002).

Cortisol administration to healthy subjects produces cognitive impairments similar to those seen in depression (Newcomer et al. 1999; de Quervain et al. 2000). In a recent study repeated administration of cortisol to healthy young men led to an impairment in recognition accuracy associated with alterations in the neural correlates of episodic memory retrieval, as assessed using an event-related potential (ERP) technique (McAllister-Williams and Rugg 2002).

The aim of the current study was to investigate the effect of repeated DHEA administration in a group of healthy young men on salivary cortisol concentrations and mood as well as exploring effects on the neural correlates of episodic memory retrieval using an identified ERP technique to that used to explore the effects of the repeated cortisol administration (McAllister-Williams and Rugg 2002). To detect brain regions activated during the cognitive task, low-resolution brain electromagnetic tomography (LORETA) was used (Pascual-Marqui et al. 1994; Pascual-Marqui et al. 1999). We hypothesised that DHEA would decrease cortisol concentrations, improve memory and lead to qualitative alterations in neuronal activity related to episodic memory retrieval.

Material and Methods

Subjects

The study population consisted of 24 healthy male volunteers aged between 18 and 40, recruited by advertisement from the local population. All were right-handed as assessed using Briggs' modification of Annett's (1967) handedness inventory (Briggs and Nebes 1975). The inclusion criteria required that subjects had an IQ of ninety or more as assessed by the National Adult Reading Test (NART) and be fluent in English in order to be familiar with all the words used in the experiment. Subjects were excluded if they had any significant past or current medical history, or any personal or first-degree family history of psychiatric illness. Baseline mood was assessed using the Beck Depression Inventory (BDI) (Beck et al. 1961) and subjects were not included if they scored 8 or more. They were required not to be taking any medication with the exception of Paracetamol (Acetaminophen). Subjects provided written informed consent prior to participation and they were reimbursed for their time and expenses. Ethical approval was obtained from the Newcastle and North Tyneside Local Research Ethics Committee.

Experimental Design

A double-blind placebo-controlled crossover design was used. Electroencephalographic (EEG) recordings were made from each subject during two separate visits following a seven-day course of 150 mg DHEA, or placebo, twice daily (i.e. a total daily dose of 300 mg). The treatments were administered in a random, balanced, order, with at least a four-week interval between treatment periods in order to exclude any carry-over effects of DHEA and minimise the learning effect

of the memory test. Subjects were asked to record the time they took medication and the duration and quality of sleep in a logbook.

Participants attended the Department of Psychiatry, the Royal Victoria Infirmary (RVI), Newcastle upon Tyne at 08:50 h. They were given breakfast and decaffeinated tea or coffee. The last dose of treatment was administered at 09:00 h, followed by the placement of an electrode cap on the scalp for EEG recordings. Visual analogue scale (VAS) measures were administered and the subjects were requested to report any adverse and/or beneficial effect of treatment they may have noticed during the last week. The purpose of the experiment and the instructions were explained to the subjects thoroughly.

DHEA and Cortisol Assay

Four saliva samples were collected 1 day prior to each visit at 1200, 1600, 2100 (just before the evening dose of medication) and 2200h. A further five saliva samples were collected on the day of testing at 0900 (baseline before last dose of medication), 0930, 1000, 1100 and 1230 h. Samples were collected by passive drooling (spitting into a plastic tube), without using aids to salivation or swabs. Cortisol and DHEA concentrations in the saliva samples were assayed using a coated tube radio-immunoassay (RIA) kit obtained from M P Biomedicals (Tyne & Wear, UK). Intra-assay variations for cortisol and DHEA were 6.2% and 8.3%, and inter-assay variations 3.0% and 4.2%, respectively.

Visual Analogue Scale (VAS)

Visual analogue scales (VASs) were used to assess subjective feelings of mood, well-being, memory, sexual drive, appetite and alertness. The VAS measures consisted of a 10 cm bar with "best" and "worst" indicated at its extremities for each variable.

Experimental Items for ERP Procedure

These were identical to material employed in previous studies (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002). In brief, stimuli consisted of low frequency (1-7 per million) words selected from Kucera and Francis corpus (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 0.5º and a maximum horizontal angle of 2.8º. Subjects were exposed to two different study/test lists on each of the two recording sessions.

Episodic Memory Task

Subjects were informed that the aim of the experiment was to investigate memory for spoken words. 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 encoding 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 performed to enhance the encoding process. The mapping of task to gender was counterbalanced across subjects.

The study phase was followed by a period of 15 minutes rest, during which the subject's attention was distracted and then the test phase was conducted. First, an asterisk appeared on the screen for one second 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 as to whether this was an old word they had heard during the study phase or a new one, using the thumb of either their left or right hand. A question mark appeared on the screen following the subject's response for 2.5 seconds and they were instructed that when they saw if the word was old they should indicate the gender of the voice that spoke the word and respond 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 to ensure that there was no correlation between the hands used for old/new and male/female judgement. The total time including orientation/practice study-test block and two experimental study-test blocks was approximately 75 min.

ERP Recording

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 mastoid processes, with the left mastoid electrode as a reference to all channels and ERPs were algebraically reconstructed off-line to represent recordings with respect to an average mastoid reference. Vertical EOG was recorded between electrodes placed below each eye and an electrode placed on the nasion. Horizontal EOG was recorded between electrodes placed on the outer canthus of the left and right eyes. EEG and EOG were filtered with a bandpass of 0.01-100 Hz and sampled at a rate of 6 ms per point for an epoch of 1536 ms beginning 102 ms before the onset of words presented in the test phase.

Average ERPs were generated for each subject for recognised old words attracting correct source judgements, and for correctly identified new items. To maximise the number of trials available for averaging, a blink-correction procedure was employed utilizing vertical EOG recordings. Any trial containing residual artefact was rejected if any channel, except VEOG, had a voltage deflection greater than ±75μV. To maintain an acceptable signal/noise ratio, a lower limit of 20 artefact-free trials per subject per visit per response category was set.

Source Localisation of the Electric Activity

LORETA, a source localisation technique 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 cortex is modelled as 2394 voxels using the digitized Talairach atlas (Talairach J and Tournoux P 1988), with a spatial resolution of 0.343 cm^3 (Pascual-Marqui et al. 1999). LORETA depends on a smoothness assumption according to which neighboring neuronal populations 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 but with some dispersion. In recent years, accumulating literature has shown LORETA localisation to be consistent with functional magnetic resonance imaging (fMRI) results (Seeck et al. 1998). However, the validity of LORETA solutions, particularly localisation of small and deep electrical generators, such as the hippocampus has been questioned (Grave de Peralta Menendez et al. 2000; Phillips et al. 2002; Fontanarosa et al. 2004). As a consequence, the results of LORETA in this study were treated with caution and simply an adjunct to topographical analysis of the ERP data.

Statistical Analysis

All values are quoted as means ± 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). To identify time periods of statistical difference between ERP scalp maps associated with different conditions, topographic analysis of variance (TANOVA) was conducted to calculate the probability of dissimilarity for each response at 6 ms intervals from -102 to 1434 ms relative to stimulus presentation. This procedure is a non-parametric randomisation test computing statistical significance for each pair of maps, correcting for multiple comparison (Thomas and Holmes 2002). Following identification of the statistically significant differences in scalp activity by TANOVA, LORETA was utilised to identify underlying neural generators during the same time period. A LORETA image was generated within the significant time period for each cortical voxel. 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.

Results

Subjects' mean age was 23.6±5.1 years (range 18-34) and their IQ was 109.8±6.7 (range 100-123). Subjects had no mood complaint with a BDI of 1.7±1.5 (range 0-5). Nineteen out of twenty-four subjects were non-smokers, while the other five smoked less than six cigarettes per day.

Salivary DHEA and Cortisol Concentrations

The average salivary concentrations of DHEA following active treatment and placebo were 1450.5±979.1 pg/ml and 691.4±474.3 pg/ml, respectively. ANOVA incorporated all nine saliva samples revealed a significant treatment effect ($F(18, 1)= 36.7$; $p<0.0001$) (see Fig 1a). There was also a significant effect of time ($F(71.4, 4.0)=2.5$; $p<0.05$); however no significant drug-by-time interaction was found ($p>0.1$).

Salivary cortisol concentrations showed the expected diurnal rhythm with placebo administration (see figure 1b). Overall salivary cortisol concentrations were not significantly different following DHEA administration ($F(18,1)=0.14$; $p>0.1$). However, post-hoc exploration of the data using paired t-tests suggested that DHEA led to a reduction in evening cortisol concentrations (2100 and 2200 h. samples) compared to placebo (1.6mmole/l vs 3.2mmole/l $p<0.05$ and 0.8mmole/l vs 2.1mmole/l $p<0.1$ respectively; see figure 1b).

DHEA Tolerability, Effects on Sleep and Subjective Ratings

DHEA was well tolerated and there was no significant difference between side effects of DHEA and placebo treatments. There was no difference in either sleep duration (7.2±1.07 vs. 7.3±1.05 hours) or quality ratings (64.5±15 vs. 65.7±14.6) between the week that DHEA and placebo were administered respectively.

VASs were only available for 16 subjects. DHEA administration significantly improved subjective mood ($t(15)= -2.5$, $p<0.05$) and memory ($t(15)= -2.1$ $p< 0.05$) but had no effect on the other VAS measures (see table1).

Episodic Memory Performance

A previous study using identical study and test stimuli found no significant effect of the sex of the voice on response accuracy or speed (Wilding and Rugg 1996). Consequently all behavioural analysis was performed on data collapsed across gender of voice speaking the items at study. In line with previous studies (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002), trials in which words were correctly judged new will be 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 (DHEA vs. placebo) and a between-subject factor of the visit the drug was administered (first vs. second). There was no significant effect of visit on either recognition or recollection, indicating no learning effect. There was no significant effect of DHEA treatment on recognition ($p>0.1$; figure 2a), though there was a significant effect on recollection ($p<0.01$)

(figure 2b), reflecting a general improvement in performance following DHEA administration compared with placebo.

ERP and LORETA Analysis

In line with previous studies, only ERPs associated with CR and HH responses were analysed. Other types of responses occurred at too low a frequency to provide sufficient numbers of trials to generate reliable average ERP waveforms. Previous work using the same stimuli found no effect of the gender of the study voice on the ERP wave forms (in line with a lack of effect on the behavioural responses; (Wilding and Rugg 1996) and so ERPs were collapsed across study voice.

Four subjects were excluded from ERP analysis due to poor quality EEG recordings with movement artefacts that could not be corrected. Grand averages of the ERPs for the HH and CR response categories from the 20 subjects following treatment with placebo are illustrated in figure 3a while figure 3b illustrates ERPs after DHEA. The ERPs shown in both figure 3a and figure 3b show the well-documented “old/new” effect (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002). In both figures, from around 400 ms post stimulus, the HH ERPs are more positive going than CR ERP.

A *priori*, it was decided to quantify the ERP data by measuring, with respect to the mean of the pre-stimulus baseline, the mean amplitudes of four consecutive latency regions, 200-500, 500-800, 800-1100 and 1100-1400 ms post stimulus, as done previously (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002). ANOVA

was used to analyse data from all active 29 electrodes. In addition, an ANOVA was conducted on four clusters of the electrodes, three each in the left anterior (FP1, F7 and F3), right anterior (FP2, F8 and F4), left posterior (O1, P7 and P3) and right posterior quadrants (O2, P8 and P4) chosen priori on the basis of previous data demonstrating the "old/new" effect (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002). These analyses were conducted on the mean amplitudes of HH and CR waveforms for each of the four latency periods described above.

Analysis of the all 29 active electrode sites revealed a significant effect of response (HH vs. CR) for both the 500-800 ms (1.7 vs. 1.07 μv; $F(1,19)= 4.56$ $p<0.05$) and 1100-1400 ms (0.56 vs. 0.01 μv; $F(1,19)= 5.49$ $p<0.05$) latency regions (see figure 3a and 3b). There was a significant effect of drug (DHEA vs. placebo) between 1100-1400 ms (0.01 vs. 0.56 μv; $F(1,19)= 5.49$ $p<0.05$) and a trend for an effect between 800-1100 ms (1.21 vs. 1.71 μv; $F(1,19)= 3.19$ $p<0.1$) post stimulus. There was however, only a trend for an interaction between drug and response between in the 200-500 ms and 800-1100 ms ($p<0.1$) latency regions.

Analysis of the four quadrants found a significant response by location (i.e. anterior vs. posterior) interaction between 500 and 800 ms and 1100 and 1400 ms latency regions, due to the "old/new" effect being more positive posteriorly in the earlier periods and anteriorly in the later period. This data is consistent with the late posterior negativity (LPN) slow wave previously identified in source memory tasks (reviewed by Johansson and Mecklinger 2003). There was also a significant response by hemisphere (right vs. left) interaction between 1100 and 1400 ms due to the

"old/new" effect being more positive on the right, as described previously (Wilding and Rugg 1996; McAllister-Williams and Rugg 2002). A main effect of drug was found between 1100 and 1400 ms with waveforms being more negative after DHEA ($p<0.05$). However, there was no significant drug by response interaction, indicating that the effect of DHEA was independent of response type.

The electrical source of activity recorded on the scalp related to episodic memory retrieval was examined with LORETA by comparing ERPs associated with HH and CR responses in the placebo condition. Firstly, a TANOVA was conducted to identify time periods of statistical difference. This revealed HH and CR related potentials to be consistently significantly different between 684 and 768 ms post-stimulus ($p<0.05$ corrected for multiple comparisons). Secondly, LORETA source localisation solutions for this time period for HH and CR related ERPs were statistically compared on a voxel-by-voxel basis. As illustrated in figure 4a, LORETA images following placebo treatment demonstrated highly significant difference between HH and CR comparisons, which was maximal in the hippocampus in association with successful recollection between 684 and 768 ms post stimulus ($t = 5.04$; $p<0.001$). In a similar way following DHEA treatment, LORETA current density values associated with HH and CR showed that successful recollection was associated with maximal activation in the insula ($t = 5.05$ $p<0.01$), as shown in figure 4b.

To examine the effect of DHEA on the neural correlates of episodic recollection, mean amplitudes of ERPs associated with CR were subtracted from those associated

with HH responses (HH-CR). Subsequently, subtracted ERPs following DHEA and placebo were analysed using LORETA. TANOVA revealed significant difference between topographic maps following DHEA and placebo between 380 and 438 ms post stimulus ($p< 0.05$). Voxel-wise LORETA comparisons revealed a trend for an effect of DHEA treatment due to differentially higher activation of the anterior cingulated cortex (ACC) compared to placebo ($p=0.06$), as illustrated in figure 5.

Discussion

The most important findings of this study are the improvement of mood and memory and the possible differential activation of ACC in the episodic memory task following repeated oral administration of DHEA in healthy young men. The study revealed that DHEA improved subjective ratings of mood in young healthy male subjects, which extends previous findings of mood improvement in elderly subjects and depressed patients (Wolkowitz et al. 1999; Wolf and Kirschbaum 1999). The study also showed that DHEA improved memory both subjectively, as measured by VAS, and objectively as measured by episodic memory recollection.

DHEA is being used in some countries, particularly the USA, by many people as an over-the-counter food supplement with unsupported recommendation of 50mg/day for men and 25mg/day for women, aiming to increase plasma concentrations of DHEA to those seen in young adults (Huppert and van Niekerk 2001). Wide discrepancies have been found in previous studies investigating the effect of DHEA administration on memory in humans. Since a continuous decline of DHEA concentrations occurs with ageing (Orentreich et al. 1984; Gray et al. 1991), most DHEA administration studies

have been conducted in the elderly using physiological doses. In general, almost all previous studies investigating the effects of DHEA treatment on neurocognitive function have failed to show significant improvement or have been somewhat inconsistent in their findings. In healthy elderly subjects, a two-week course of DHEA (50 mg/day) has been shown to cause a trend towards improvement in mood, well-being and visual memory in women but not men (Wolf et al. 1997). A similar DHEA paradigm in elderly subjects under acute psychosocial stress showed DHEA (50 mg/day) treatment impaired declarative memory but improved attention (Wolf et al. 1998). Longer durations of treatment (13-week course of DHEA, 50 mg/day) in a normal elderly population demonstrates association between high concentration of DHEA and less confusion, reduced anxiety and better mood; but DHEA has no significant benefits on cognition (van Niekerk et al. 2001). Our study was different to these previous investigations of repeated DHEA administration due to our subjects being young healthy males. To our knowledge, the only previous study to test the effects of DHEA on cognitive function in healthy young subjects used a single-dose of DHEA (300 mg) and found no effect on memory (Wolf et al. 1997). In our study, we have used a similar relatively high (pharmacological) dose (150mg b.d.) over a one week period and demonstrated that this has beneficial effects on memory, suggesting that positive benefits of DHEA may require both pharmacological doses and repeated administration.

DHEA treatment modified ERPs associated with episodic memory recollection and led to a possible differential activation of ACC between 380 and 438 ms post stimulus. This early effect, if replicated, is of particular interest since ACC has been implicated in attention, executive function and memory processing (Morgane et al.

2005). The ACC has extensive connections with the hippocampus and it is possible that the differential activation of ACC following DHEA treatment may be due to pre-hippocampal memory processing that enhanced successful recollection.

To our knowledge, this is the first study to use LORETA source localisation of an episodic memory task. In the placebo condition, episodic recollection was associated with activation of the hippocampus, which is recognised as playing an important role in many forms of memory. However, following DHEA treatment, the site of maximal activation during recollection was another limbic structure, the insula. This has previously been shown in event-related fMRI studies to be activated during an episodic recollection task (Konishi et al. 2000). The apparent difference in source localisation of episodic memory between placebo and DHEA pre-treatment conditions may simply reflect the low spatial resolution of LORETA. This is supported by the fact that at the time these limbic structures were activated, there was no significant difference in the HH-CR subtracted ERP waveforms between DHEA and placebo treatments.

It is difficult to determine the mechanisms of action of DHEA that led to beneficial effects on memory. Data from animal studies have revealed that DHEA has a variety of actions on the central nervous system (CNS), including the promotion of neurogenesis in the hippocampal dentate gyrus, neuroprotection and reduction of neurodegeneration (Majewska 1995; Lapchak et al. 2000; Lapchak and Araujo 2001; Karishma and Herbert 2002). DHEA also has effects on several neurotransmitter receptor systems known to impact on memory function. For example, it acts as an

agonist at glutamate NMDA receptors and it is known that NMDA receptor antagonists impair memory (Wolf and Kirschbaum 1999). Furthermore, DHEA shows functional antagonistic properties at $GABA_A$ receptors and agonistic properties at sigma receptors (Majewska 1992; Monnet et al. 1995) with many studies demonstrating that both $GABA_A$ antagonists and sigma agonists may enhance memory (Wolf and Kirschbaum 1999). DHEA is a precursor of oestrogens and androgens, and so it is also possible that memory improvement with DHEA was, in part, due effects of sex steroids on cognition (Hirshman et al. 2004). An increase in gonadal steroids has been shown in previous studies following DHEA administration (Morales et al. 1994; Morales et al. 1998). Memory-enhancing effects of gonadal steroids have also been frequently reported following administration of oestradiol (Phillips and Sherwin 1992; Hogervorst et al. 2000) and testosterone (Cherrier et al. 2001; Aleman et al. 2004). Since the present study did not measure plasma concentrations of testosterone and oestradiol it is not possible to comment on whether the observed effects of DHEA were in fact medicated following its conversion to these cannot be decided whether these steroids led, or at least contributed to the effect of DHEA seen in the current study.

The finding of a beneficial effect of DHEA on mood is necessarily speculative since only a subjective rating scale was used in this study. However, this effect may have resulted from DHEA reported ability to modulate 5-HT systems; for example enhancing the firing rate of 5-HT neurons (Robichaud and Debonnel 2004). Improvement in mood has been noted in depressed patients following treatment with DHEA (Wolkowitz et al. 1999), although other studies have found no improvements in perimenopausal mood symptoms (Barnhart et al. 1999).

Findings from this study demonstrate that repeated administration of DHEA produces long-lasting elevation of salivary DHEA concentrations and possibly a decrease of evening salivary cortisol concentrations, though since this was only shown with a post-hoc t-test, the finding needs to be replicated. In a placebo controlled study, Wolf and colleagues (1997) found that a single dose of DHEA led to an immediate decrease in cortisol concentrations. Interestingly, in that study DHEA was administered during the evening, i.e. during the cortisol trough. Our results reveal that repeated DHEA treatment does not change morning cortisol concentrations and the decrease in evening cortisol concentrations does not appear to simply be due to the acute effect of DHEA administration since the largest effect was seen immediately prior to taking the evening dose. If confirmed, these findings may be of great interest since trough cortisol concentrations in particular are elevated in depression (Young et al. 1994). A reverse of this may underlie the reported benefits of DHEA in depression (Wolkowitz et al. 1999).

The potential therapeutic implications of these findings need to be considered with considerable caution. Firstly, it is difficult to extrapolate the current positive effects of DHEA on memory and mood from this study in young healthy individuals to an elderly population with memory impairments. The current study investigated the effects of supraphysiological doses in a population with high baseline endogenous DHEA concentrations. It is unclear what dose would be required to produce similar effects, if these are possible, in a population with lower baseline DHEA concentrations. Secondly, the use of such high doses of DHEA as used here over the long term, could theoretically lead, via metabolism into active sex steroids, to adverse

effects, such as enhanced hormone-sensitive tumour growth (Wolkowitz et al. 2003). As a result future investigations need to proceed with caution. This is despite a report that DHEA administration at pharmacological (but not physiological) concentrations inhibits angiogenesis, which is implicated in the pathologies of neoplasm, both in vitro and in vivo (Varet et al. 2004).

In summary, this study has shown that DHEA treatment led to enhancement in recollection accuracy associated with a modification in the electrophysiological correlates of episodic memory retrieval. In addition, DHEA improved subjective memory and mood, and decreased evening cortisol concentrations. These unique findings are the first to show such beneficial effects of DHEA in healthy young males.

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Table1. The mean ± standard deviation of visual analogue scale measures following DHEA and placebo (in mm.). DHEA improved subjective mood and memory (*= $p<0.05$) but had no effect on the other VASs. Note that the larger the number, the better the subjective rating of each variable.

	Placebo	DHEA
Mood *	71.9 ±16.2	78.9±10.6
Memory *	71±14.2	76±14.6
Sexual Drive	74.8±17.3	77.4±16.6
Appetite	71.1±19.5	74.4±16.3
Alertness	70.9±16.1	69.1±10.8
Well-being	75.7±18.1	77.3±12.7

FIGURE LEGENDS

Fig. 1 A. Salivary DHEA concentrations following DHEA (solid line) and placebo (dashed line). Concentrations were measured on day 7 and day 8 of treatment. Arrows show time of last two treatment administration. **B.** Salivary cortisol concentrations following DHEA (solid line) and placebo (dashed line). All other details are as described for Fig. 1A

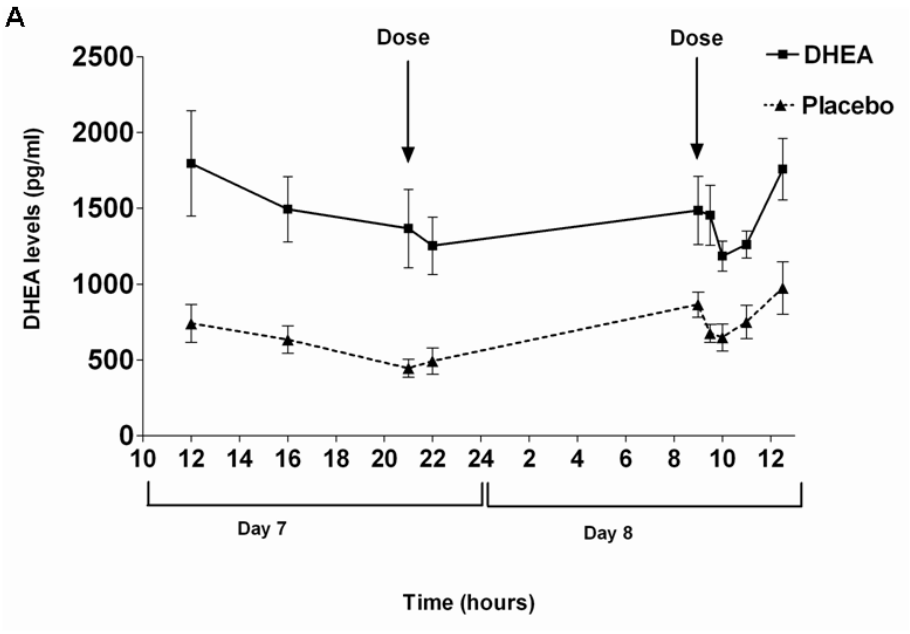
Fig. 2 Episodic memory performance following DHEA and placebo treatments **A.** Memory recognition i indexed by the probability of a correct recognition of an old item (H) minus the probability of falsely referring to a new item as old (FA); see text for details. **B.** Episodic memory recollected as demonstrated by pHH/H (probability of accurate recollection given recognition of an old item; see text for details)

Fig. 3 Grand average ERP waveforms from representative electrode sites: F4 (right anterior), F3 (left anterior), P4 (right posterior) P3 (left posterior). CR related ERPs are shown with a solid line, while HH related ERPs are shown with a dashed line. **A.** CR and HH related ERP grand averages following placebo administration. **B.** CR and HH related ERP grand averages following DHEA administration.

Fig. 4 Statistical nonparametric LORETA maps of activation during recollection as assessed by the comparison of HH with CR responses. (L=left; R=right; A=anterior; P=posterior). **A.** LORETA localisation of HH vs. CR responses following placebo administration. Maximal activation is in the hippocampus ($p<0.001$) **B.** LORETA localisation of HH vs. CR following DHEA administration. Maximal activation is in Broadman Area 13 (Insula, Sub-lobar $p<0.01$)

Fig. 5 LORETA localisation of subtraction ERP waveforms (HH-CR) following DHEA and placebo administration between 380 and 438 ms post stimulus. Maximal activation is seen in Broadman Area 25 (Anterior Cingulate, Limbic Lobe $p=0.06$)

Figure 1.


A
Dose
Dose
DHEA
Placebo
DHEA levels (pg/ml)
2500
2000
1500
1000
500
0
10 12 14 16 18 20 22 24 2 4 6 8 10 12
Day 7
Day 8
Time (hours)

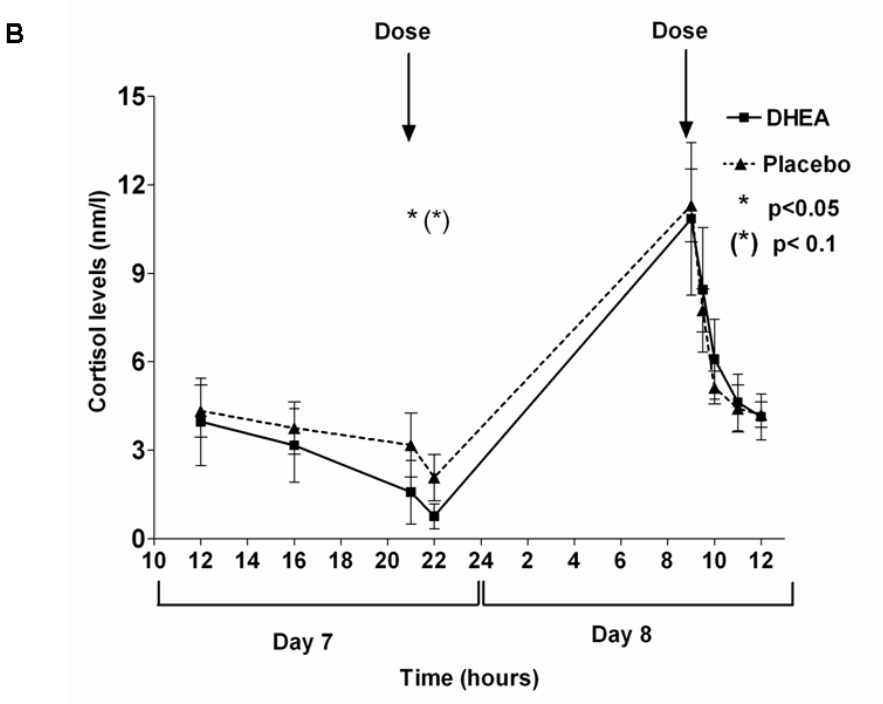
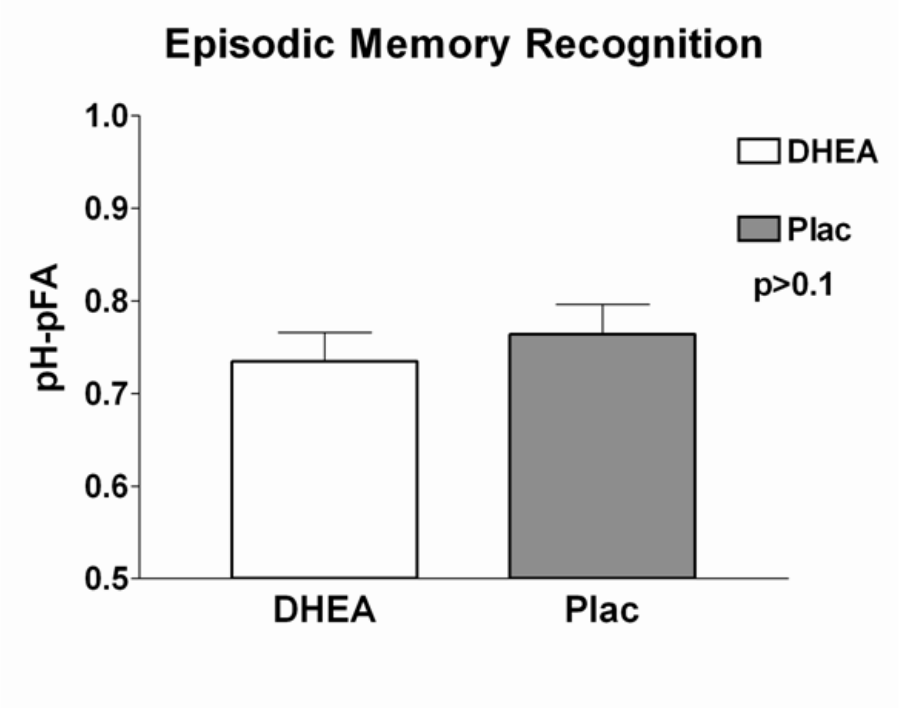

B
Dose
Dose
DHEA
Placebo
* p<0.05
(*) p< 0.1
* (*)
Cortisol levels (nm/l)
15
12
9
6
3
0
10 12 14 16 18 20 22 24 2 4 6 8 10 12
Day 7
Day 8
Time (hours)

Figure 2


Episodic Memory Recognition
pH-pFA
1.0
0.9
0.8
0.7
0.6
0.5
DHEA
Plac
p>0.1
DHEA
Plac

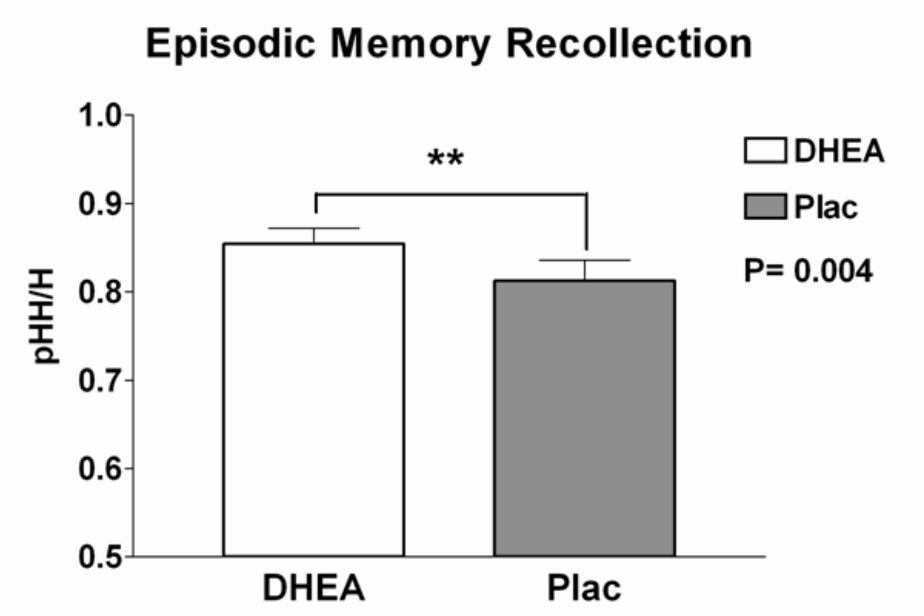

Episodic Memory Recollection
pHH/H
1.0
0.9
0.8
0.7
0.6
0.5
**
DHEA
Plac
P= 0.004
DHEA
Plac

Figure 3.

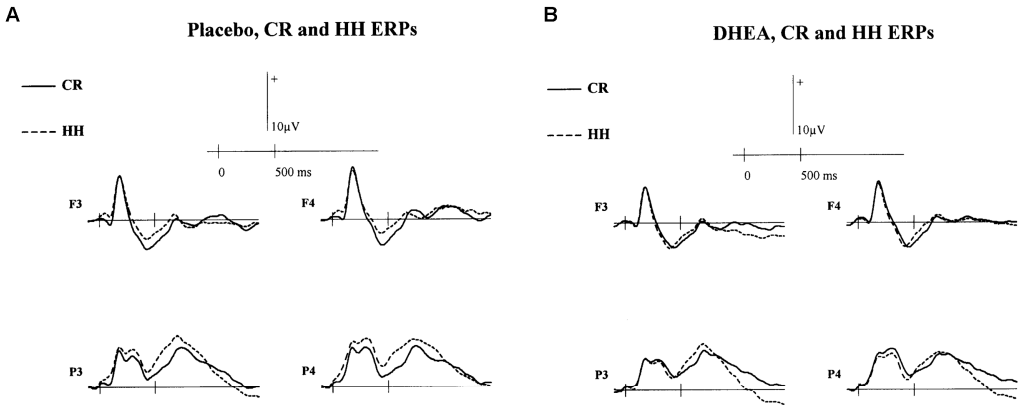

A
Placebo, CR and HH ERPs
CR
HH
10μV
0
500 ms
F3
F4
P3
P4
B
DHEA, CR and HH ERPs
CR
HH
10μV
0
500 ms
F3
F4
P3
P4

Figure 4.

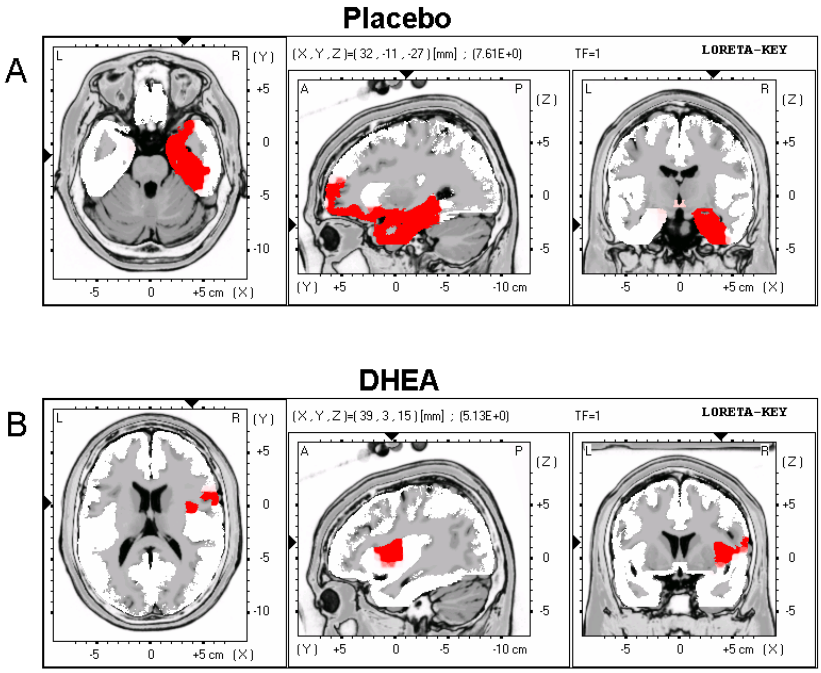
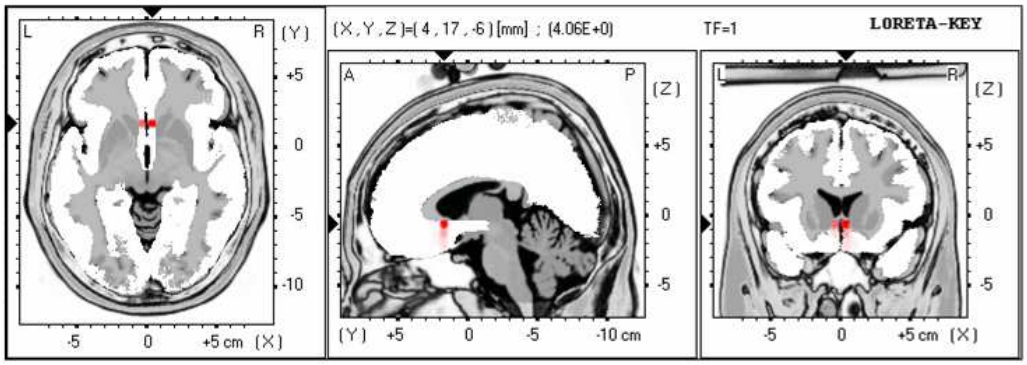

A
Placebo
(X,Y,Z)=(32, -11, -27) [mm] ; (7.61E+0)
TF=1
LORETA-KEY
B
DHEA
(X,Y,Z)=(39, 3, 15) [mm] ; (5.13E+0)
TF=1
LORETA-KEY

Figure 5.


L
R
(Y)
+5
0
-5
-10
-5
0
+5 cm (X)
(X,Y,Z)=(4 , 17 , -6) [mm] ; (4.06E+0)
TF=1
LORETA-KEY
A
P
(Z)
+5
0
-5
(Y) +5
0
-5
-10 cm
L
R
(Z)
+5
0
-5
-5
0
+5 cm (X)