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Abstract

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Key Words: cortisol; sulphate dehydroepiandrosterone; memory; first-episode psychosis; stress

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1. Introduction

Widespread cognitive impairment is a core characteristic of psychotic disorders that is evident at the first episode of psychosis (FEP), with prominent deficits observed in information processing speed, executive functioning and verbal memory (Mesholam-Gately et al., 2009). Emergence of cognitive impairment occurs well before the onset of the first psychotic episode, even in early childhood (Fusar-Poli et al., 2012), suggesting aberrant neurodevelopment (Bora and Murray, 2014). Cognitive impairments generally remain relatively stable for many years after the first episode (Bozikas and Andreou, 2011). Longitudinal studies have shown that relative to other cognitive domains, poor verbal memory is particularly associated with poorer clinical outcomes, such as incomplete symptomatic recovery and relapse (Barder et al., 2013; Benoit et al., 2014; Bozikas and Andreou, 2011; Chang et al., 2013). Impaired verbal memory is also a significant predictor of poorer long-term functional outcomes in both clinical high-risk (Lin et al., 2011) and first-episode cohorts (Chang et al., 2013).

The neurobiological mechanisms mediating memory impairment in psychotic disorders are not clearly understood. Cognitive function, particularly learning and memory, is known to be sensitive to stress (Aas et al., 2011; Teicher et al., 2002). Elevated stress or chronic exposure to stress can lead to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in vulnerable individuals (Lupien et al., 2009). The HPA-axis regulates both neuroendocrine (i.e., glucocorticoid release) and behavioural stress responses (Smith and Vale, 2006). Levels of cortisol, a glucocorticoid hormone released from the adrenal gland in response to stress, is a common measure of HPA-axis activity. Dehydroepiandrosterone (DHEA) and its sulphate form DHEA(S) are neurosteroids produced by the adrenal gland that exert anti-glucocorticoid effects. In this regard, DHEA represents additional neurosteroid mechanisms that are of relevance to the regulation of the HPA-axis (Crowley and Girdler,

2014). DHEA(S) is released together with cortisol in response to stress and is known to counteract the negative effects of cortisol in the brain (Kimonides et al., 1999), exerting neuroprotective properties (Wolkowitz et al., 2001). Under conditions of chronic stress, DHEA(S) levels decline (while cortisol levels are maintained), resulting in an elevated cortisol:DHEA(S) ratio (Wolkowitz et al., 2001). It has been suggested that this may result in attenuated buffering of the cognitive-impairing effects of cortisol (Maninger et al., 2009).

Prolonged exposure to elevated levels of cortisol is shown to have detrimental effects on the structural and functional integrity of the brain, particularly involving hippocampal atrophy and memory impairment, respectively. Studies in rats have shown that chronic exposure to stress or corticosterone (the rodent equivalent of cortisol) leads to atrophy of dendrites in the hippocampus (Watanabe et al., 1992), which is accompanied by impaired performance on hippocampal-dependent memory tasks (Luine et al., 1994). A relationship between cortisol, the hippocampus and memory function has been demonstrated across a range of human conditions, treatment with steroids, normal aging, and stress-related psychiatric disorders (Corcoran et al., 2003; Sapolsky, 2000; Walder et al., 2000). Furthermore, higher DHEA(S) levels in military personnel predicted superior cognitive performance under stress (Morgan et al., 2009). A higher cortisol:DHEA(S) ratio is associated with cognitive decline (Kalmijn et al., 1998), and poorer visuospatial memory performance in healthy older adults (van Niekerk et al., 2001), and higher distraction during a working memory task in healthy female adults (do Vale et al., 2014). Following anti-glucocorticoid treatment (decreasing cortisol levels), an increase in hippocampal volume and improvement in memory is observed (Starkman et al., 2003), indicating that cortisol-induced memory deficits may be reversible. While DHEA(S) supplementation has been shown to have cognitive (working memory) enhancing properties in rodents (Maninger et al., 2009;

Wolf and Kirschbaum, 1999), clinical trials of DHEA(S) in healthy older adults have produced conflicting findings (Huppert et al., 2000).

HPA-axis hyperactivity is often reported in schizophrenia populations (Corcoran et al., 2003), including elevated plasma cortisol and adrenocorticotropic hormone levels (Lammers et al., 1995; Ryan et al., 2004), and increased corticotropic-releasing hormone concentrations in cerebrospinal fluid (Banki et al., 1987). HPA hyperactivity may be potentiated by attenuated negative feedback inhibition of HPA function in schizophrenia (Lammers et al., 1995). In particular, impairments in hippocampal-mediated suppression of HPA function may play a key role. Studies have reported an inverse correlation between cortisol levels and performance on hippocampal-dependent memory tasks (Newcomer et al., 1998; Walder et al., 2000) and a positive correlation between circulating DHEA(S) and memory performance (Harris et al., 2001; Silver et al., 2005) in chronic schizophrenia. Clinical trials of DHEA augmentation in people with chronic schizophrenia have reported a non-significant improvement in memory (Strous et al., 2007) and found DHEA(S) levels to be a positive predictor of cognitive functioning (Ritsner and Strous, 2010).

The initial psychotic phase may also be associated with dysregulation of the HPA-axis, although fewer studies have been conducted and findings have been mixed. For example, studies have found elevated levels of circulating adrenocorticotropic hormone and cortisol (Ryan et al., 2004), reduced cortisol levels (Phassouliotis et al., 2013), and no difference between FEP and healthy controls groups in levels of cortisol, DHEA(S) or their ratio (Garner et al., 2011). However, in the latter study decreases in cortisol and the cortisol:DHEA(S) ratio over 12 weeks were associated with improvements in depression and psychotic symptoms (Garner et al., 2011). The relationship between stress hormones and memory function in early psychosis has received limited investigation and analyses have been cross-sectional. One study found that blunted (i.e., abnormal) cortisol levels following

awakening were associated with more impaired verbal memory and processing speed in FEP (Aas et al., 2011). In contrast, Labad et al. (2016) found that an increased cortisol awakening response was associated with poorer verbal memory and processing speed and a more flattened diurnal cortisol slope was associated with poorer visuospatial working memory in females with early psychosis. Dexamethasone suppression ratio was associated with better visual memory in both males and females (Labad et al., 2016). In another study, higher afternoon cortisol levels at treatment entry were significantly related to impaired verbal memory performance at in hospitalized males with first-episode schizophrenia (Havelka et al., 2016).

As poor verbal memory is present at the first episode of psychosis and associated with a poorer illness course, the relationship between stress hormones and memory in early psychosis is a critical area of investigation. The current study aimed to investigate the relationship between circulating stress hormones (cortisol, DHEA(S) and their ratio) and verbal memory function prospectively in people with FEP during the initial 12 weeks of treatment, compared to healthy controls. To our knowledge this is one the first studies to prospectively investigate stress hormones and cognitive functioning in drug-naïve or minimally-treated FEP patients compared to sex and age-matched healthy control participants. We hypothesised that higher cortisol, lower DHEA(S) and a higher cortisol:DHEA(S) ratio would be associated with poorer verbal memory performance in minimally-treated FEP patients and healthy controls at baseline and 12-weeks follow-up. We also explored whether a reduction in the cortisol:DHEA(S) ratio during the initial 12 weeks of treatment would correlate with improved memory performance in the FEP group at the 12-week follow-up assessment.

2. Methods

2.1 Participants

Participants for the current study came from an overarching study examining stress and HPA-axis functioning in FEP and the relationships with clinical, cognitive and brain structure variables (Garner et al., 2011; Phassouliotis et al., 2013; Reniers et al., 2015). Neuroleptic-naïve or minimally-treated FEP patients were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC) at Orygen Youth Health, Melbourne, Australia. Inclusion criteria were based upon the entry criteria for EPPIC as follows: aged 15-25 years, experiencing a first episode psychotic disorder as per DSM-IV criteria, and resident in the EPPIC catchment (North/North-Western suburbs of metropolitan Melbourne). Exclusion criteria were >10 days of treatment with any psychotropic medication, IQ<70, neurological or brain impairment, any significant medical illness including impaired thyroid function, polydipsia, asthma, diabetes or chronic fatigue syndrome, steroid medications, and shift work. Females taking an oral contraceptive were also excluded due to potential interactions between oral contraceptives and androgen levels. Participants received standard EPPIC treatment over the 12-week study period, including low dose antipsychotic medication and intensive case management and psychosocial rehabilitation.

Healthy control (HC) participants were recruited from similar socio-demographic areas through advertisements and acquaintances of the FEP participants. Exclusion criteria included a current or past history of psychiatric illness or any psychiatric illness in the immediate family, in addition to the exclusion criteria described for the FEP group. Details of the previous two menstrual cycles were recorded for all female participants, however as we previously found no differences between menstrual cycle phase and biological stress measures (Garner et al., 2011) these were not included in the current analysis. The study was approved by the Melbourne Health Human Research and Ethics Committee. After complete

description of the study, written informed consent was obtained from participants or a parent or guardian when appropriate.

2.2 Clinical Assessments conducted at Baseline

To confirm inclusion the patient edition of the Structured Clinical Interview for DSM-IV for Axis I disorders (SCID-I/P) was administered to FEP participants and the Structured Clinical Interview for DSM-IV Non-Patient edition (SCID-I/NP) was administered to control participants. The Perceived Stress Scale (PSS) (Cohen et al., 1983) was used to examine subjective levels of stress in both groups. Body mass index and tobacco use in the previous month were collected. The following clinical assessments were also completed with FEP participants only: Brief Psychiatric Rating Scale extended version 4 (BPRS) (Ventura et al., 1993), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) and Social and Occupational Functioning Scale (SOFAS) (Goldman et al., 1992). The BPRS positive symptom subscale (BPRS-P) consisted of the 4 core psychotic items: suspiciousness, hallucinatory behaviour, disorganised thinking and unusual thought content.

2.3 Blood Collection and Analyses

Blood sampling occurred between 9.00 and 10.00am upon entry to the study and at 12 weeks follow-up. Blood (20mL) was withdrawn by venepuncture into tubes containing SST or EDTA for the collection of serum and plasma, respectively. Serum cortisol levels were analysed by Gribbles Pathology (Melbourne, Australia) and plasma DHEA(S) levels were analysed by Melbourne Pathology (Melbourne, Australia). DHEA(S) was measured, as opposed to DHEA, because it is more stable with a longer half-life and less prone to changes with the circadian rhythm (Wolf and Kirschbaum, 1999).

2.4 Cognitive Assessment

Assessment of attention, working memory and verbal learning and memory was performed with both groups at baseline and 12 weeks. The cognitive assessment was

conducted as close to the time of blood sampling as possible. The Wide Range Achievement Test-Third Edition (WRAT-3)-Reading subtest was administered at baseline to estimate premorbid IQ. The Digit Span - digits forward subtest from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) was used as a measure of immediate auditory-verbal attention span. Digit Span - digits backward and Letter-Number Sequencing total score from the WAIS-III were used to measure auditory verbal working memory. Verbal learning and memory was assessed using an experimental verbal paired associate learning (PAL) test based on a paradigm used by Savage et al. (2002), which demonstrated sensitivity to dysfunction in medial temporal lobe structures. Individuals with chronic schizophrenia have demonstrated impaired performance on the task (Gallucci et al., 2001) and the current version of the task was designed to load minimally on attention and working memory. The task involves initial pre-learning of two lists of 8 words over 3 trials of exposure and free recall, followed by 3 trials of exposure and cued recall for 8 inter-list arbitrary pairings of the words. The imageability of the words varied across pairs (e.g., 'horse-forest', 'busy-limit'). Cued recall of the word pairs was tested after a 20-minute delay. Alternate versions of the test were used at the two time points to minimise practice effects. All tests were administered and scored according to standardised instructions, and raw scores were used in the analysis.

2.5 Statistical Analysis

Independent-samples t-tests were used to compare the two groups with respect to baseline stress hormones and cognitive measures. Repeated-measures analysis of variance (ANOVA) with a group factor (FEP and HC) and a time factor (baseline and week 12) was used to examine change in stress hormone levels and cognitive performance from baseline to 12 weeks. To investigate whether stress hormone levels were associated with attention, working memory and learning and memory performance, general linear model analysis was employed with each of the cognitive measures as the dependent variable in turn, and each of

the stress hormone measures as the independent variable in turn. The analysis was carried out on the combined sample with age and sex as covariates (as stress hormones can differ based on age and sex (Wudy et al., 2007)) to examine the general relationship between stress hormones and cognitive performance. The group factor (FEP and HC) was also included. This was to allow the examination of the group by stress hormone interaction, which would indicate whether there were any differences between the FEP and HC group in the relationship between stress hormones and cognitive performance. We also ~~examined~~ explored if the results changed after adjusting for premorbid IQ (presented in Supplementary Tables; caution in interpreting these tables is recommended because measurement of premorbid IQ based on a reading test may be problematic in adolescents and young adults who are yet to complete their education and whose education will have been disrupted due to their psychosis). ~~The group factor (FEP and HC) was also included. This was to allow the examination of the group by stress hormone interaction, which would indicate whether there were any differences between the FEP and HC group in the relationship between stress hormones and cognitive performance.~~ The analysis was conducted using the relevant baseline values, week 12 values and the change in values (week 12 minus baseline). Alpha-level was set at .05. There was no adjustment for multiple comparisons because such correction is only required when carrying out joint hypothesis testing (Rothman et al., 2008), and this was not our aim. IBM SPSS Statistics 22 and S-PLUS 6.1 were used to conduct the analyses.

3. Results

3.1 Sample Characteristics at Baseline

Thirty-five FEP and 23 HC participants were included in the current study. Table 1 shows the baseline characteristics of the two groups. The FEP participants were significantly younger and had a lower level of education and estimated premorbid IQ compared to the HCs. FEP participants also reported significantly higher levels of perceived stress and were

more likely to have used tobacco in the previous month. DSM-IV diagnoses of FEP participants were: schizophreniform disorder (n=15), schizoaffective disorder (n=2), delusional disorder (n=1), psychotic disorder NOS (n=3), bipolar disorder I with psychotic features (n=1), major depressive disorder with psychotic features (n=4), substance-induced psychotic disorder (n=2), and specific psychotic diagnosis was unavailable for 7 participants who were unable to complete the SCID, but had a confirmed 'first-episode psychosis' according to clinical notes. Among the FEP participants, prior to baseline blood collection 12 were prescribed antipsychotic medication, 9 were neuroleptic naïve and 14 had missing information. Of the 12 who were taking medication, the mean number of days on antipsychotics prior to baseline blood collection was 4.3 (SD 1.5, minimum 2, maximum 7).

3.2 Change in Stress Hormone Levels and Cognitive Performance over 12 weeks

For the FEP group, the time difference between the baseline blood sampling and cognitive assessment ranged from 1 to 15 days, with 47% being conducted within 4 days. For the control group, the two procedures were conducted within 0 to 9 days, with 91% being within 4 days. Table 2 shows the results for levels of cortisol, DHEA(S) and the cortisol:DHEA(S) ratio at baseline and 12 weeks. No significant differences were found between the two groups on any of the stress hormone measures at baseline. There were no significant changes in any of the stress hormone levels from baseline to 12 weeks in either group (cortisol p=.770; DHEA(S) p=.167; cortisol:DHEA(S) p=.449), nor were there any group by time interactions (cortisol p=.993; DHEA(S) p=.227; cortisol:DHEA(S) p=.535).

Table 3 shows the cognitive performance of the two groups at baseline and 12 weeks. At baseline, the FEP participants performed more poorly on all cognitive tasks relative to the HC group, with effect sizes in the medium to large range. Repeated-measures ANOVA indicated there was a significant main effect of time (i.e., change between baseline and 12 weeks) for performance on digit span backwards, which improved over 12 weeks (p=.045)

and immediate paired associate learning, which worsened over 12 weeks (p=.019). There were no significant effects of time on the other cognitive measures. There were no significant group by time interactions for any of the cognitive measures (all p>.05).

3.3 Relationship between stress hormone levels and cognitive functioning

3.3.1 Baseline

There were no significant relationships between cognitive performance and stress hormone levels at baseline (all p>.05; Supplementary Table). There was a significant group by DHEA(S) interaction for digit span forward (immediate attention) (p=.0493), showing that higher DHEA(S) was associated with better performance in HC (r=.41), but poorer performance in the FEP group (r=-.1622) (Figure 1).

3.3.2 Follow-up (12 weeks)

There was a significant negative relationship between digit span forward (immediate attention) and the cortisol:DHEA(S) ratio (partial r=-.42; p=.02) at 12 weeks. There were no significant group by stress hormone interactions in association with cognitive performance (all p>.05; Supplementary Table).

3.3.3 Change in stress hormone levels and cognitive performance over 12 weeks

The relationship between change in stress hormones and cognitive performance over 12 weeks (week 12 minus baseline) was explored. There was a negative association between changes in DHEA(S) and immediate paired associate learning (partial r=-.43; p=.025) over 12 weeks, such that increased levels of DHEA(S) was associated with worsening of paired associate learning. There were no significant group by stress hormone interactions (all p>.05; Supplementary Table).

4. Discussion

Understanding how stress and HPA-axis (dys)function are associated with the course of early psychosis could have important implications for the development of therapeutic

interventions that can target the HPA-axis and cognitive sequelae. To our knowledge, this is the first prospective study to investigate the longitudinal relationship between circulating stress hormones (cortisol, DHEA(S)) and cognitive performance in people with FEP during the initial 12 weeks of treatment, compared to healthy controls. The key findings can be summarised as follows: (1) At baseline the FEP and HC groups did not differ in levels of cortisol, DHEA(S) or their ratio and no significant group differences were observed in the change of these hormone concentrations over the 12-week follow-up. (2) Consistent with previous research (Mesholam-Gately et al., 2009), the FEP group performed significantly below HC on all cognitive measures at baseline. While working memory improved and immediate paired associate learning declined over 12 weeks in the overall group, there were no significant group differences in change in cognitive performance over this period. (3) Cortisol levels were not related to memory or other cognitive performances in either group. (4) Baseline DHEA(S) was associated with baseline attention span (digit span forward). Specifically, higher DHEA(S) was positively associated with attention scores in HCs, but negatively associated with attention in FEP individuals (Figure 1). Further, change in DHEA(S) was negatively associated with change in immediate paired associate learning over the 12-week period in both groups. (5) At 12 weeks, there was a negative correlation between the cortisol:DHEA(S) ratio and attention (digit span forward) in both groups. (6) Exploration of the relationship between changes in the cortisol:DHEA(S) ratio during the initial 12 weeks of treatment and memory performance in FEP yielded nonsignificant findings.

Previous studies have demonstrated associations between stress hormone levels and memory (and other cognitive) functioning in people with psychosis. Higher cortisol has been associated with poorer memory in medicated chronic schizophrenia samples (Newcomer et al., 1998; Walder et al., 2000). In FEP studies, higher afternoon cortisol levels have been associated with poorer verbal memory (Havelka et al., 2016), and both blunted (Aas et al.,

2011) and increased (Labad et al., 2016) awakening cortisol responses have been associated with poorer memory and processing speed. In contrast, cortisol levels were not associated with cognitive functioning in either group in the current study. In Walder et al. (2000), cortisol was measured hourly over three hours and the strongest negative association between memory performance and cortisol was evident at hour three. A study by Silver et al. (2005) found no relationship between memory performance and a single morning blood cortisol level in a schizophrenia sample. Given previous research in FEP has suggested a blunted awakening cortisol response in the context of increased cortisol levels throughout the day (Mondelli et al., 2010), it is possible that our single morning measurement did not adequately capture the likely complex relationship between cortisol and memory in FEP (also see Aas et al., 2011; Labad et al., 2016). Thus, frequency and timing of blood sampling may partly explain these different findings. Furthermore, the largest study in FEP to date by Labad et al. (2016) found that the relationship between cortisol awakening response and cognitive performance was evident only in women, highlighting sex as an important moderating factor. Additionally, Newcomer et al. (1998) found that dexamethasone treatment (a synthetic glucocorticoid) did not decrease verbal memory performance in people with schizophrenia, although it did in HCs, suggesting reduced functional (brain) sensitivity to acute effects of cortisol in schizophrenia.

Lower DHEA(S) has also been associated with poorer cognition in medicated chronic schizophrenia samples (Harris et al., 2001; Ritsner and Strous, 2010; Silver et al., 2005). In this FEP study at baseline, the hypothesised positive relationship between DHEA(S) and attention was observed in HC, whereas a negative association was evident in the FEP group. Thus, despite similar levels in both groups, DHEA(S) did not have a positive relationship with attention span in this FEP sample. Also unexpectedly, a higher cortisol:DHEA(S) ratio was associated with better attention span at 12 weeks in both groups. Our findings are in

contrast to previous research in chronic schizophrenia, which found that circulating DHEA(S) was positively associated with sustained attention (explaining 6.9% variance) (Ritsner and Strous, 2010), memory (r=.42-.51) (Harris et al., 2001; Silver et al., 2005) and executive functioning (*r*=.50) (Silver et al., 2005). Furthermore, the cortisol:DHEA(S) ratio was previously found to be negatively associated with visual memory and executive functioning (explaining 3.7% and 3.6% variance, respectively) (Ritsner and Strous, 2010). Interestingly, change in DHEA(S) was negatively associated with change in immediate paired associate learning over the 12-week period in both groups, that is, an increase in DHEA(S) over time was associated with a decrease in memory performance. Again, this finding was unexpected and in contrast to previous research in chronic schizophrenia (Ritsner and Strous, 2010). It is important to note that DHEA levels were not measured in the current study, thus the possibility of altered DHEA in the FEP individuals and an association with cognitive performance cannot be ruled out.

Compared to the current sample, these previous chronic schizophrenia studies reported much lower DHEA(S) levels and a higher cortisol:DHEA(S) ratio, likely indicative of phase of illness (mean length of illness 13-14 years) and/or age (mean 36-48 years) of participants (Harris et al., 2001; Ritsner and Strous, 2010; Silver et al., 2005). Chronic patients may show a large variation in HPA function due to long-term medication and more variable degrees of exposure to stress, whereas in FEP there is a much shorter duration of treatment and illness. These factors may moderate the relationship between neurosteroids and cognition in psychosis. Given that FEP participants had hormone levels within the range of HCs, it could be argued that the stress related to the onset of illness (as well as previous stress exposure) was not ‘chronic enough’ (given it is still very early on in the course) to cause significant long-lasting down-regulation of DHEA(S). Indeed, their cortisol levels were not abnormally high or low relative to HCs. It has also been previously suggested that a lack of a

group difference and relative stability in stress hormone levels over 12 weeks in FEP and HCs may be indicative of an absence of a neurosteroid response to the initial stage of psychosis in the FEP participants (Garner et al., 2011). Longitudinal studies that include measures of chronic stress, such as hair cortisol levels will be more informative.

The relative stability of cognitive impairment in the FEP group over the follow-up period is consistent with previous research and perhaps unsurprising given that 12 weeks is a relatively short period to expect significant cognitive change. Most studies that have shown cognitive improvement following FEP (over and above practice effects) had follow-up periods of 1 year or longer (Bora and Murray, 2014; Bozikas and Andreou, 2011). Poorer verbal memory at baseline has been associated with a diagnosis of schizophrenia relative to affective psychoses (Zanelli et al., 2010), a lack of symptomatic remission (Benoit et al., 2014; Chang et al., 2013), and early psychotic relapse (Barder et al., 2013) in FEP, but in these studies marked memory impairment was evident early, without significant memory decline thereafter (Benoit et al., 2014; Chang et al., 2013). In order to better understand the neurobiological mechanisms (such as HPA-axis function) associated with memory impairment or decline, subgroup-level analyses of those with the poorest outcomes may be needed. This should also include further longitudinal research in those at clinical high risk for psychosis given memory impairment usually emerges before the first psychotic episode (Fusar-Poli et al., 2012).

Strengths of this study include recruitment of a carefully selected minimally-treated FEP sample and prospective observation over the initial treatment period, including repeat cognitive assessment. There are also limitations that warrant mentioning. The sample size could be considered relatively small, though it is larger than many previous studies (Aas et al., 2011; Harris et al., 2001; Havelka et al., 2016; Newcomer et al., 1998; Silver et al., 2005; Walder et al., 2000) and it is worth noting that recruiting and retaining minimally-treated

unwell FEP participants is challenging. For the main aim of this study, which was to examine whether the relationship between stress hormones and verbal memory function differ between FEP individuals and healthy controls, a sample size of about 110 would be needed to explain a large effect (for 80% power and 5% significance level). Thus, lack of power could be a possible reason for some of the non-significant findings. Furthermore, given the small sample, separate analysis on males and females could not be conducted and would have been preferable to statistically controlling for sex. Second, measurement of stress hormone levels at one time point is likely to be less reliable than the diurnal rhythm. Time of awakening was not recorded in the current study, which may have been a potential confounder. Possible group differences in diurnal stress hormone levels that have been previously shown in FEP (Aas et al., 2011; Mondelli et al., 2010) may have been present. Assessment of hormone levels after blood sampling might have been confounded by the anticipatory stress of the venipuncture procedure and perceived stressfulness of blood-taking was not assessed. Furthermore, as blood samples were often not taken on the same day as the cognitive assessment this may have affected the relationships observed. Nevertheless, it is important to note that stress hormone levels remained quite stable in both groups over the two time-points. Additionally, the FEP participants had a range of psychosis diagnoses and for some the diagnosis was unknown. Thus, apart from the short follow-up period, the chances of detecting significant relationships may have been reduced due to heterogeneous clinical presentations. The treatment received over the 12-week period was not recorded and therefore could not be taken into account in the analysis (e.g., effect of antipsychotics on neuroendocrine markers). Finally, administration of the cognitive tasks (including the alternate forms of the PAL task) between time-points was not counter-balanced to minimise possible order effects; this may have explained the decline in immediate paired associate learning in both groups over the 12 week period.

While we observed some significant relationships between stress hormones and cognitive performances in FEP and HCs, most observations were non-significant or in the unexpected direction. In particular, the findings of the current study suggest a possible relationship between DHEA(S) and attention and immediate paired associate learning over the first 12 weeks of treatment in FEP. This study supports the need for the inclusion of neurobiological markers such as stress-related hormones in neuropsychological research. Further investigation with larger samples, at different phases of illness, and over longer follow-up periods is needed to determine the likely complex relationship between HPA-axis and memory functioning in psychosis.

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Table 1. Baseline characteristics of the two groups.

	FEP (n=35)	**HC (n=23)**	**p-value***
Age (mean, SD)	20.3 (2.5)	22.1 (1.8)	0.002
Sex (n, % male)	26 (74.3)	18 (78.3)	>0.999
Education (n, % completed Year 12)	14 (40.0)	22 (95.7)	<.001
Premorbid IQ (mean, SD)	95.6 (11.7)[b]	102.6 (11.0)	0.032
Body Mass Index (mean, SD)	24.0 (6.1)[c]	21.7 (3.3)	0.090
Tobacco use in past month (n, % yes)	24 (70.6)[d]	5 (22.7)[e]	0.001
PSS total (mean, SD)	33.8 (8.5)[a]	22.0 (6.5)	<.001
BPRS psychotic subscale (mean, SD)	15.0 (4.2)[b]		
SANS total (mean, SD)	21.7 (12.5)[b]		
SOFAS (mean, SD)	55.2 (9.6)		

FEP=first-episode psychosis; HC=healthy controls; SD=standard deviation; PSS=Perceived Stress Scale; BPRS=Brief Psychiatric Rating Scale; SANS=Scale for the Assessment of Negative Symptoms; SOFAS=Social and Occupational Functioning Scale

*Age, premorbid IQ, Body Mass Index, PSS Total: t-test p-value; sex, education, tobacco use: Fisher's exact test p-value.

[a]n=30; [b]n=31; [c]n=29; [d]n=34; [e]n=22

Table 2. Cortisol, DHEA(S) and their ratio at baseline and 12 weeks.

		FEP	**HC**	**p-value**
Cortisol (nmol/L; mean, SD)	Baseline	486.4 (137.3)	479.9 (132.8)	0.860
	12 weeks	494.2 (114.7)	488.1 (107.3)	
DHEA(S) (nmol/L; mean, SD)	Baseline	9340.6 (2735.8)	8839.1 (3785.1)	0.591
	12 weeks	11147.4 (3518.7)	8856.2 (3723.3)	
Cortisol:DHEA(S) ratio (mean, SD)	Baseline	5.6 (2.3)	6.5 (3.1)	0.281
	12 weeks	4.9 (4.2)	6.4 (2.8)	

Table 3. Cognitive functioning at baseline and 12 weeks.

		FEP	HC	p-value*	Effect Size
Attention					
Digit span forward (raw)	Baseline	9.3 (2.5)	10.9 (2.3)	.015	0.63
	12 weeks	10.3 (2.1)	11.8 (2.1)		
Working Memory					
Digit span backward (raw)	Baseline	5.4 (1.7)	8.7 (2.6)	<.001	1.24
	12 weeks	6.4 (2.3)	9.4 (1.9)		
Letter number sequencing (raw)	Baseline	9.2 (3.5)	12.1 (2.8)	.001	0.81
	12 weeks	10.1 (2.6)	12.6 (1.3)		
Verbal Learning and Memory					
Immediate PAL total[a]	Baseline	15.3 (7.3)	22.9 (3.8)	<.001	1.07
	12 weeks	13.3 (4.4)	19.0 (3.7)		
Delayed PAL total[b]	Baseline	4.7 (2.4)	7.2 (1.0)	<.001	1.08
	12 weeks	4.9 (2.4)	6.2 (1.8)		

*t-test p-value; PAL=paired associate learning; [a]Maximum score=24; [b]Maximum score=8

Figure Legend

Figure 1. Baseline digit span forward by DHEA(S) for each group.

C=Control
F=FEP
DHEAS=sulphate dehydroepiandrosterone

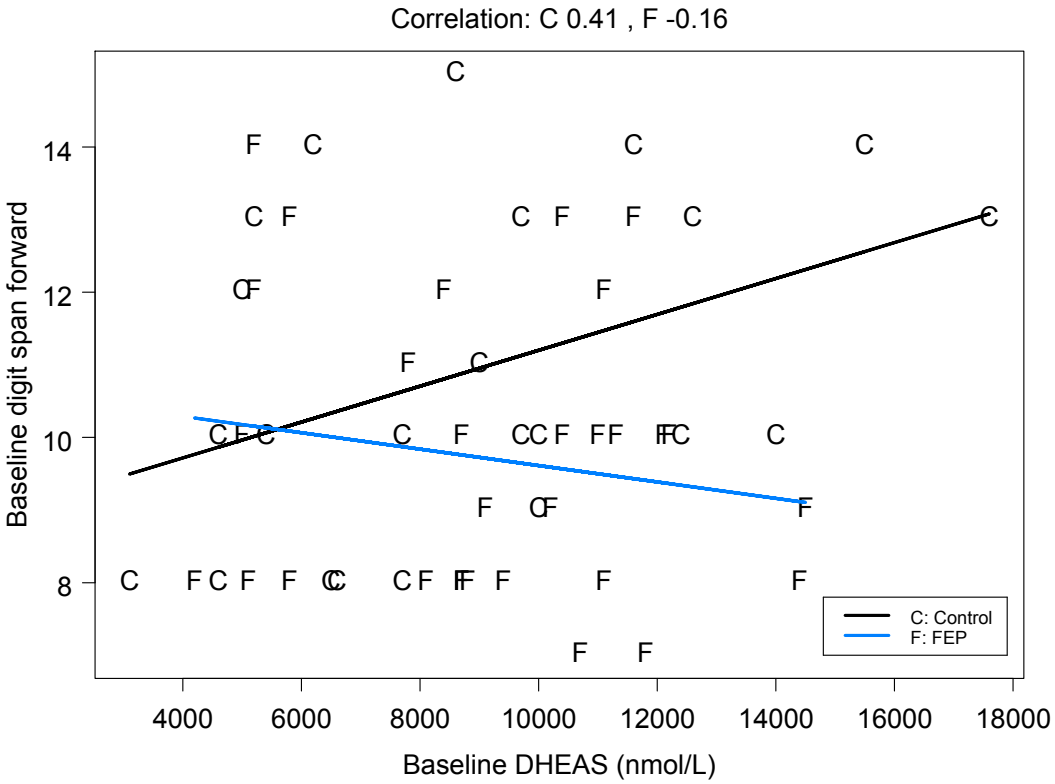

Figure 1. Baseline digit span forward by DHEA(S) for each group.

Supplementary Tables

P values for primary analysis and when premorbid IQ is added as a covariate.

Baseline					
Cognitive Test	**Hormone**	**Adjusting for group, age, sex**	**Group x Stress hormone interaction**	**Adjusting for premorbid IQ**	**Group x sex interaction adjusting for premorbid IQ**
Attention					
Digit span forward (raw)	Cortisol	0.904	0.055	0.712	0.014
	DHEAS	0.639	0.049	0.433	0.002
	Cortisol:DHEAS	0.798	0.707	0.290	0.185
Working Memory					
Digit span backward (raw)	Cortisol	0.122	0.611	0.617	0.986
	DHEAS	0.114	0.698	0.165	0.234
	Cortisol:DHEAS	0.964	0.516	0.545	0.119
Letter number sequencing (raw)	Cortisol	0.356	0.069	0.078	0.018
	DHEAS	0.978	0.301	0.516	0.251
	Cortisol:DHEAS	0.702	0.916	0.101	0.769
Verbal Learning and Memory					
Immediate PAL total	Cortisol	0.378	0.634	0.250	0.289
	DHEAS	0.987	0.587	0.541	0.406
	Cortisol:DHEAS	0.286	0.902	0.766	0.235
Delayed PAL total	Cortisol	0.813	0.420	0.744	0.588
	DHEAS	0.746	0.309	0.304	0.383
	Cortisol:DHEAS	0.644	0.422	0.232	0.071

PAL=paired associate learning; DHEAS=sulphate dehydroepiandrosterone

12 Weeks					
Cognitive Test	**Hormone**	**Adjusting for group, age, sex**	**Group x Stress hormone interaction**	**Adjusting for premorbid IQ**	**Interaction adjusting for premorbid IQ**
Attention					
Digit span forward (raw)	Cortisol	0.058	0.736	0.178	0.975
	DHEAS	0.290	0.689	0.114	0.273
	Cortisol:DHEAS	0.020	0.754	0.008	0.211
Working Memory					
Digit span backward (raw)	Cortisol	0.131	0.314	0.350	0.388
	DHEAS	0.453	0.088	0.607	0.006
	Cortisol:DHEAS	0.531	0.457	0.480	0.035
Letter number sequencing (raw)	Cortisol	0.669	0.585	0.940	0.499
	DHEAS	0.829	0.495	0.549	0.389
	Cortisol:DHEAS	0.484	0.969	0.207	0.923
Verbal Learning and Memory					
Immediate PAL total	Cortisol	0.403	0.610	0.689	0.797
	DHEAS	0.517	0.676	0.574	0.995
	Cortisol:DHEAS	0.713	0.883	0.692	0.469
Delayed PAL total	Cortisol	0.667	0.175	0.924	0.155
	DHEAS	0.903	0.562	0.659	0.393
	Cortisol:DHEAS	0.431	0.527	0.304	0.378

PAL=paired associate learning; DHEAS=sulphate dehydroepiandrosterone

Change over 12 weeks					
Cognitive Test	**Hormone**	**Adjusting for group, age, sex**	**Group x Stress hormone interaction**	**Adjusting for premorbid IQ**	**Interaction adjusting for premorbid IQ**
Attention					
Digit span forward (raw)	Cortisol	0.757	0.184	0.345	0.515
	DHEAS	0.814	0.446	0.662	0.481
	Cortisol:DHEAS	0.421	0.348	0.221	0.559
Working Memory					
Digit span backward (raw)	Cortisol	0.985	0.462	0.974	0.251
	DHEAS	0.717	0.111	0.608	0.114
	Cortisol:DHEAS	0.726	0.786	0.833	0.556
Letter number sequencing (raw)	Cortisol	0.114	0.881	0.055	0.658
	DHEAS	0.810	0.173	0.659	0.202
	Cortisol:DHEAS	0.259	0.221	0.319	0.157
Verbal Learning and Memory					
Immediate PAL total	Cortisol	0.877	0.436	0.397	0.559
	DHEAS	0.026	0.393	0.046	0.458
	Cortisol:DHEAS	0.227	0.706	0.114	0.384
Delayed PAL total	Cortisol	0.910	0.392	0.304	0.877
	DHEAS	0.910	0.167	0.758	0.173
	Cortisol:DHEAS	0.891	0.893	0.510	0.669

PAL=paired associate learning; DHEAS=sulphate dehydroepiandrosterone