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# Stress hormones and verbal memory in young people over the first 12 weeks of treatment for psychosis

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ABSTRACT

*Aims:* Memory impairment in psychosis may be mediated through detrimental effects of hypothalamic-pituitary-adrenal (HPA) axis function. This study prospectively investigated the relationship between cortisol, sulphate dehydroepiandrosterone (DHEA(S) and cortisol: DHEA(S) ratio and memory in 35 first-episode psychosis (FEP) patients during the first 12 weeks of treatment and 23 healthy controls (HC).

*Methods:* Morning blood sampling and tests of attention, working memory and verbal memory occurred at baseline and 12-week follow-up.

*Results:* FEP and HC groups did not significantly differ in levels of cortisol, DHEA(S) or their ratio at baseline or over 12-weeks. The FEP group performed significantly below HC on all cognitive measures at baseline and over 12-weeks. Cortisol levels were unrelated to cognition in both groups. At baseline, DHEA(S) was positively associated with attention in HCs, but negatively associated with attention in FEP participants. Change in DHEA(S) was negatively associated with change in memory over 12-weeks in both groups. At 12-weeks, there was a negative correlation between the cortisol: DHEA(S) ratio and attention in both groups.

*Conclusions:* These findings are mostly in contrast to findings in chronic schizophrenia. Investigation at different illness phases and over longer-follow-up periods is required to determine the complex relationship between HPA-axis and memory functioning in psychosis.

## 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).

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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-