The association between the cortisol awakening response (CAR) and neurocognitive impairments in first episode psychosis patients and ultra high-risk individuals

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CONTRIBUTION OF AUTHORS

As the first author of both manuscripts, I (Shamira Pira), made a significant contribution to the formulation of hypotheses, research design, data collection and analyses, and the writing of both manuscripts.

Dr. Marita Pruessner provided substantial contributions to research design, data analysis, interpretation of findings and content structure for both manuscripts.

Dr. Srividya Iyer has provided substantial contributions to data collection and analysis, interpretation of findings, and revisions of content for both manuscripts.

Gina Marandola contributed significantly to data acquisition.

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ABSTRACT

Background: Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in psychotic disorders. Abnormal levels of the HPA axis hormone, cortisol, are associated with various cognitive processes and cognitive deficits are a key feature of psychosis. The cortisol awakening response (CAR) has been shown to be abnormal in first episode psychosis (FEP) patients but has not been explored in individuals at ultra high-risk (UHR) for developing psychosis. Objectives: The objectives of the following set of studies were to examine the relationship between the CAR and cognitive function in FEP patients and in UHR individuals. In addition, based on established sex differences in both HPA axis activity and psychosis, the effect of sex on this relationship was also explored. Methods: Eighty-two FEP patients, 28 individuals at UHR for psychosis, and 31 community controls were recruited to participate in the two studies. Saliva samples were collected to assess the CAR and a neuropsychological battery was administered to determine performance on six cognitive domains. From these, a global cognition score was also calculated. Results: FEP patients, but not UHR individuals, had a blunted CAR compared to controls and male FEP patients had a more blunted CAR than female FEP patients. A more blunted CAR was associated with a more severe deficit in verbal memory and a lower global cognition score only in female FEP patients. Conclusion: The results suggest that although UHR individuals show deficits in certain cognitive domains, the CAR remains in tact, and there is no association between the two. However, a blunted CAR plays a role in cognitive function for female FEP patients. This may have implications for time and gender specific interventions aimed at stabilizing HPA axis activity.
RÉSUMÉ

Contexte: La dérégulation de l'axe hypothalamo-hypophyso-surrénalien (HHS) a été observée dans les troubles psychotiques. Des niveaux anormaux de cortisol, une des hormones de l'axe HHS, sont associés à divers processus cognitifs et les déficits cognitifs sont un élément clé de la psychose. Des études démontrent que la sécrétion de cortisol au réveil (SCR) est anormale dans le premier épisode psychotique (PEP) des patients, mais n'a pas été explorée chez les personnes à très haut risque (THR) de développer une épisode de psychose. Objectifs: Les objectifs de ces diverses études étaient d'examiner la relation entre la SCR et la fonction cognitive chez les patients PEP et chez les personnes THR. En dépit des différences de sexe connues sur l'axe HPA et la psychose, l'effet du sexe sur cette relation n'a pas été étudié. Méthodes: Quatre-vingt-deux patients PEP, 28 individus à THR pour la psychose, et 31 contrôles communautaires ont été recrutés pour participer dans les deux études. Des échantillons de salive ont été prélevés pour évaluer la SCR et une batterie de tests neuropsychologiques a été administrée pour déterminer les performances sur six domaines cognitifs. De ceux-ci, un résultat cognitif global a également été calculé. Résultats: Les patients PEP, mais pas les individus THR, avaient une SCR atténuée par rapport aux témoins contrôles et les patients masculins PEP avaient une SCR plus atténuée que les patients PEP féminin. Une SCR plus atténuée a été associée à un déficit plus sévère de la mémoire verbale et un résultat inférieur de la cognition globale uniquement chez les patients PEP féminins. Conclusion: Bien que les individus THR présentent des déficits dans certains domaines cognitifs, les résultats montrent que la SCR reste intacte et qu'il n'y a aucun lien entre les deux. Toutefois, une SCR atténuée joue un rôle dans la fonction cognitive chez les patients PEP féminins. Cela
peut avoir des implications pour les interventions spécifiques au sexe et au temps visant à stabiliser l’activité de l'axe HHS.
CHAPTER 1

Background and Objectives

1.1. Neurocognition and Psychosis

Psychotic disorders are among the most disabling and chronic psychiatric illnesses with schizophrenia having a median incidence rate of 15.2 per 100,000 persons and a median lifetime morbid risk of 7.2 per 1000 persons (McGrath et al., 2008). These disorders usually present with a varying combination of 3 dimensions of symptoms: reality distortion (hallucinations and some types of delusions), disorganization (inappropriate affect, poverty of content of speech, and formal thought disorder), and negative symptoms or psychomotor poverty (blunted affect, poverty of speech, and lack of spontaneous movements) (Liddle, 1987; Malla et al., 1993). However, psychotic disorders were initially conceptualized as more than just the presence of these categories of symptoms. Indeed, the eminent psychiatrist, Emil Kraeplin, who first termed the condition *dementia praecox* or “premature dementia” (Kraeplin, 1896), placed a great deal of emphasis on the early onset and progressive intellectual deterioration as core features of the illness. Following this, a psychiatrist by the name of Eugen Bleuler coined the term *schizophrenia* meaning “splitting of the mind” (Bleuler, 1911) to describe the same set of heterogeneous clinical symptoms. But at a fundamental level, he too believed it to be a disorder that disrupted cognitive processes. Since the time of these initial observations, cognitive impairments have become a widely accepted feature of psychotic illnesses, and as such, have generated a great deal of interest.
Individuals with psychosis display a broad range of impairments across many neurocognitive domains including attention, verbal memory, executive function, and processing speed (Dickinson et al., 2007; Gold & Harvey, 1993; Heinrichs & Zakzanis, 1998). Deficits in these areas have been reported as early on in the course of illness as the presentation of the first episode of psychosis (FEP) (Mesholam-Gately et al., 2009; Zanelli et al., 2010), have been shown to remain stable over time (Gold, 2004), persist after the remission of positive symptoms (Bowie & Harvey, 2006) and are likely to have an impact on both clinical and functional outcome as well as quality of life (Bodnar et al., 2008; Green et al., 2000). Meta-analyses of cognitive impairments have revealed that both chronic and FEP patients perform at least one standard deviation below the mean of healthy controls (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009), although the severity of deficits depends on the nature of the sample with lower overall deficits found in epidemiologically representative samples of FEP (Townsend et al., 2001).

Furthermore, the attempt to localize impaired performance on neuropsychological tests to specific brain regions such as the frontal, temporal, hippocampal, parietal, striatal, and cerebellar functions (Dickinson & Harvey, 2009) has led to research investigating the underlying mechanisms of the cognitive deficits observed in this population. Taken together, evidence supports the idea that cognitive impairment is central to the pathophysiology of the disorder and not secondary to symptoms.

1.2. Neurocognition and Ultra High-Risk

The development of psychosis up to the presentation of a first episode is a gradual process that typically occurs during adolescence and early adulthood. It is often preceded by a period of non-specific psychiatric symptoms and/or sub threshold psychotic
symptoms retrospectively known as the “prodrome”. Norman et al. (2005) have suggested that prodromal signs of schizophrenia can be factored on to 5 dimensions: dysphoria and odd perceptual and cognitive content, impaired functioning, psychobiological changes, suspiciousness and difficulties with concentration, and irritability or aggression (Norman et al., 2005). Prospective research conducted on this period has revealed a state of ultra high risk (UHR) that is more proximal to the time of onset of psychosis (Yung et al., 1996).

Symptoms that fall into the reality distortion category are included in the widely used criteria to identify UHR individuals. These criteria include the presence of one or more of the following three characteristics: 1) experiencing sub-threshold positive psychotic symptoms 2) experiencing brief episodes of frank psychotic symptoms that have not lasted longer than a week and resolve spontaneously 3) having a first-degree relative with a psychotic disorder coupled with a 30% decrease in functioning (Phillips et al., 2002). While the existence of cognitive deficits, even at the time of the first episode, is well established, it has not been operationalized into UHR criteria. This is, in part, due to the fact that reviews conducted on studies investigating neurocognitive deficits in UHR individuals have yielded inconsistent results (Brewer et al., 2006; Pukrop & Klosterkötter, 2010). The review by Brewer et al. (2006) indicated that although high-risk cohorts perform intermediate to health controls and FEP patients on generalized neurocognitive test batteries, their performance is at a relatively normal level. Further, they also found that high-risk individuals showed deficits in more discrete functions such as olfactory identification and spatial memory than in more neuropsychologically complex areas such as verbal memory (Brewer et al., 2006). A more recent review on
this topic showed that high-risk individuals have been found to perform both at the schizophrenia level and at a close to normal level with impairments in measures of processing speed, verbal working memory, verbal memory and learning, and verbal fluency being the most convincing findings (Pukrop & Klosterkötter, 2010). However, the authors have noted that negative findings have also been reported in each one of these domains. Thus, it remains unclear when these cognitive changes emerge in the developmental course of psychotic disorders and what factors play a role in triggering and exacerbating them.

1.3. The Stress Diathesis Model

Although the exact etiology of psychotic disorders is unknown, the stress-diathesis model may be the most parsimonious one in helping us understand the onset and course of psychotic disorders (Walker et al., 2008). This conceptual framework proposes that biological vulnerability and environmental stress play complementary roles in the onset and course of psychotic illness (Nuechterlein & Dawson, 1984; Rosenthal, 1970; Zubin & Spring, 1977). Central to this model is the idea that individuals with psychosis are exposed to a higher degree of psychosocial stressors than the general population. However, there has been very little evidence to support that patients experience more major life events (Norman & Malla, 1993). It is possible though, since the stress response is contingent on an individual’s appraisal of a situation (Lazarus & Folkman, 1984), that the events experienced by patients are appraised differently than they would be by their healthy counterparts. In fact, it has been shown that daily stressors or hassles experienced by people with psychosis are more predictive of subjective distress than major life events (Norman & Malla, 1994; Norman & Malla, 1991). Although individuals with psychosis
may not experience a greater number of stressful life events, they display increased
distress and an inability to cope with the events that they do encounter (Horan et al.,
2005). Furthermore, a recent meta-analysis has concluded that exposure to early stressors
such as childhood trauma including physical, sexual, emotional, and psychological abuse
as well as neglect, parental death, and bullying are strongly associated with increased risk
for psychosis (Varese et al., 2012).

1.3.1. Hypothalamic-Pituitary-Adrenal (HPA) Axis

Most studies investigating the role of stress as a risk factor in psychiatric illnesses,
including psychosis, have focused on the hypothalamic-pituitary-adrenal (HPA) axis
because it is considered to be the major mediator of the biological stress response. Once
activated by the presence of a stressor, the hypothalamus releases corticotrophin-releasing
hormone (CRH), which signals the anterior lobe of the pituitary gland to release
adrenocorticotropic hormone (ACTH). ACTH in turn acts on the cortex of the adrenal
gland causing it to release glucocorticoids (cortisol in humans) into the body. Cortisol
binds to both mineralcorticoid receptors (MRs) and glucocorticoid receptors (GRs) which
are present in almost every tissue of the body. HPA axis activity is regulated via a
negative feedback loop. This means that at higher levels, such as those resulting from
stress exposure, circulating cortisol begins to bind to receptors in the hypothalamus and
anterior pituitary in order to inhibit activity of the axis.

HPA axis activity follows a distinct circadian rhythm (Pincus, 1943). In healthy
individuals, cortisol quickly rises and peaks within 30-35 minutes after awakening. This
peak, called the cortisol awakening response (CAR), is a reliable measure of HPA axis
activity (Pruessner et al., 1997) and has in fact, been shown to be the body’s response to the act of waking up (Wilhelm et al., 2007). An abnormal CAR has been observed in many clinical populations including individuals with depression (Bhagwagar et al., 2005; Cowen, 2010; Vreeburg et al., 2009), bipolar disorder (Deshauer et al., 2003), post-traumatic stress disorder (PTSD) (Wessa et al., 2006; Yehuda, 2005), and young men with Asperger syndrome (Brosnan et al., 2009). The CAR is thought to be distinct from diurnal cortisol levels (Clow et al., 2004; Fries et al., 2009; Wilhelm et al., 2007) which gradually decrease throughout the day reaching their lowest point soon after the onset of sleep and rise during sleep itself (Turner-Cobb, 2005).

Chronically high levels of cortisol result in adverse effects on the organ systems that have a high density of glucocorticoid receptors including the cardiovascular system (Sholter & Armstrong, 2000), the immune system (Khansari et al., 1990), and the nervous system, ultimately effecting brain function (Sapolsky, 1996).

1.3.2. The Hippocampus, the Prefrontal Cortex, and Cognition

The hippocampus is a neural structure that is part of the limbic system and a brain region that is rich with glucocorticoid receptors. As such, according to the “glucocorticoid cascade hypothesis”, increased exposure to glucocorticoids should reduce cortisol mediated feedback inhibition via the hippocampus ultimately resulting in excessive cortisol secretion whereby damaging the hippocampus (Sapolsky et al., 1986). Indeed, it has been shown that the hippocampus plays a crucial role in regulating HPA axis activity (Jacobson & Sapolsky, 1991). Chronically high levels of cortisol have been shown to have deleterious effects on the make up of this area (McEwen, 1999; Sapolsky,
Animal studies have revealed that stressors experienced by mothers during gestation can have long lasting adverse effects on the hippocampus of the offspring. For example, adult male rats that were exposed to stress during the prenatal period have a reduced number of both MRs and GRs in the hippocampus (Henry et al., 1994). Also, since the hippocampus continues to develop after birth, it remains vulnerable to the effects of childhood trauma and chronic stress. In fact, recent reviews have concluded that adults with a history of childhood maltreatment have lower hippocampal volumes (Frodl & O'Keane, 2012; Woon & Hedges, 2008). Stress experienced throughout the lifespan, from the prenatal period through to old age can have adverse effects on various brain regions and related cognitive functions (Lupien et al., 2009).

The hippocampus is also known to play a central role in memory formation. This was initially documented in a case study of a man who became amnesic following bilateral removal of the medial temporal lobe, including the hippocampus (Scoville & Milner, 1957). Research conducted since then, has been able to narrow in on the function of the hippocampus in the complex cognitive processes involved in learning and memory. It is now widely accepted that the hippocampus mediates a form of memory called declarative or explicit memory (Squire, 1992). Declarative memory encompasses the ability to recollect facts and events, which is unlike non-declarative memory for skills and habits. Specifically, studies have emphasized the role of the hippocampus in two aspects of declarative memory: episodic memory for personal experiences and acquiring factual knowledge (Eichenbaum, 2004).

As a result of the dual role played by the hippocampus in regulating HPA axis activity and mediating cognitive processes, increased stress exposure has been shown to be
related to neurocognitive impairments (Lupien & Lepage, 2001). Impairments, particularly in the areas involving learning and memory, have been noted in many clinical and nonclinical populations including those with depression (Porter et al., 2003), PTSD (Weber et al., 2005), Cushings Syndrome (Starkman et al., 1992), elderly subjects (Lupien et al., 1997), and even healthy controls administered synthetic glucocorticoids (Hsu et al., 2003).

Although majority of the initial work on the effect of stress on cognition focused on the hippocampus, recent studies have begun to highlight the involvement of other areas such as the prefrontal cortex (PFC). The PFC, like the hippocampus, is also part of the limbic circuitry and expresses a large number of glucocorticoid receptors. However, its involvement in the HPA axis regulatory feedback loop is more complex than that of the hippocampus. Where the hippocampus has a largely inhibitory effect on the axis, the effect of the PFC varies depending on specific regions (Dedovic et al., 2009; Herman et al., 2005). In addition, the PFC is known to mediate a variety of higher order functions that promote the selection and processing of information that is required to control and direct behaviour. Therefore, it is possible that stress-induced alternations in the PFC underlie executive function and processing speed related cognitive deficits.

1.4. The Neural Stress Diathesis Model

Over the years, the stress-diathesis model has become increasingly complex with investigators attempting to incorporate new research findings and advances in our understanding of the adverse effects of stress on brain function. Drawing upon findings from both human and animal literature, Walker and Diforio proposed the more
comprehensive neural stress-diathesis model (Walker & Diforio, 1997). They expanded upon how external factors and neural mechanisms interact in order to produce the set of behavioural outcomes seen in schizophrenia.

Firstly, they adopted the broader definition of stressors as events or experiences that jeopardize homeostasis (Chrousos & Gold, 1992). By doing so they were able to discuss the effect of, not only psychosocial stressors, but also prenatal and perinatal assaults on the hippocampus and the HPA axis. In fact, adverse prenatal environments such as maternal infection (Brown & Derkits, 2010) and birth complications (Cannon et al., 2002), among others, have been associated with an increased risk for the development of psychotic disorders (King et al., 2010).

In addition, they incorporated the roles of the neuroendocrine and autonomic nervous systems since these are involved in facilitating the organism’s capacity to respond to stress (McEwen, 1995). Whereby the authors were able to include the bidirectional relationship between hippocampal function and HPA axis activity in their conceptualization of the neural mechanisms that underlie psychotic disorders. In fact, recent meta-analyses have shown that patients, even at the time of the first episode, have a significantly smaller hippocampal volume (Steen et al., 2006; Vita et al., 2006). The PFC is another region shown to be compromised in individuals with psychosis (Gur et al., 2000). Furthermore, PFC volume loss has been shown in UHR individuals that convert to a full syndrome of psychosis (Pantelis et al., 2007; Sun et al., 2009; Wood et al., 2008). Moreover, deficits in prefrontally mediated tasks are the most prominent, in UHR individuals (Brewer et al., 2006) and have been shown to be predictive of conversion to psychosis from this prodromal state (Wood et al., 2008). Thus, when the
neural stress-diathesis model was revisited, the authors suggested that regulatory feedback of the HPA axis emanates from the frontal cortex, in addition to the hippocampus (Walker et al., 2008).

In additional support of the model, elevated basal cortisol levels resulting from dysregulation of the HPA axis have been reported in FEP patients (Gunduz-Bruce et al., 2007; Mondelli et al., 2010; Ryan et al., 2004). Moreover, one study has also reported an abnormal (blunted CAR) in FEP patients (Mondelli et al., 2010) as compared to healthy controls. However, our own group was unable to replicate this finding in a small sample of FEP patients (Pruessner et al., 2008) although we found that male patients showed a significantly more blunted CAR than female patients. In a later study, using a larger FEP sample, we found a more blunted CAR in patients than controls but this did not remain significant after adjusting for time of awakening (Pruessner et al., 2012). Although, basal hypercortisolemia has also been observed in UHR individuals and other prodromal groups (Thompson et al., 2007; Walker et al., 2010), no studies to date have examined the CAR in this population.

1.5. The CAR, Cognition, and Psychosis

A recent study confirmed previous findings that FEP patients display a blunted CAR compared to healthy controls (Aas et al., 2011b). They further hypothesized that there would be a relationship between HPA axis dysregulation and cognitive impairments. Indeed, they observed an association between an abnormal (more blunted) CAR and cognitive deficits in the domains of verbal memory and processing speed in FEP patients. Furthermore, although they reported a trend for higher daytime cortisol
levels in FEP patients, there was no association between this measure of HPA axis activity and cognitive function in either group. However, the possibility of a sex difference in the association between the CAR and cognitive performance has not been explored.

According to a recent review, an enhanced HPA axis response to stress appears to be part of the biological vulnerability to psychosis and can be observed prior to the onset of psychosis (Aiello et al., 2012), although few studies have examined HPA axis activity in UHR individuals. However, it remains unclear whether an abnormal CAR is detectible in this stage of the illness. Exploring the CAR in UHR individuals, would serve to establish a more complete picture of HPA axis dysregulation in this group and to discern whether an abnormal CAR also precedes the onset of illness (psychosis), therefore representing a biological risk factor, or whether it is caused by the onset of the disorder itself. Furthermore, the possibility of a relationship similar to the one observed in FEP patients between an abnormal CAR and cognitive impairment has not been investigated in this population.

1.6. Objectives

1) In the first study, we attempt to replicate previous findings of an association between dysregulation of the HPA axis, as quantified by a blunted cortisol awakening response, and cognitive function, specifically in the domains of verbal memory and processing speed, in a larger well-characterized FEP sample. Based on previous reports indicating sex differences in the CAR in this population (Pruessner et al., 2008; Pruessner et al., 2012) and suggestions that studies of the effects of stress on the brain should take
sex into consideration (Lupien et al., 2009), we investigated whether such differences also emerge in examining the putative association between CAR and cognitive function.

2) In the second study, we first examine cognitive function in our UHR group. Then we investigate the possibility that HPA axis dysregulation, in the form of an abnormal CAR, is present even earlier than at the time of the first episode, in individuals considered to be at ultra-high risk for the development of psychosis. Furthermore, we examine the relationship between the CAR and neurocognitive performance in UHR patients.
CHAPTER 2:

Methods

2.1. Treatment Setting:

First episode psychosis patients included in the first study were receiving treatment at the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal) in southwest Montreal, Quebec, Canada. This is the only specialized early intervention service for this population in the defined catchment area with no competing private or public hospital facilities. Ultra high-risk patients in the second study were recruited from the Clinic for Assessment of Youth at Risk (CAYR), which is a sub-program of PEPP-Montreal and operates as a symptom monitoring service for young individuals who are at high risk for developing psychosis.

2.2. Subjects

Subjects for these studies were recruited between 2005 and 2012 as part of a larger ongoing research project investigating stress and cortisol effects on symptom severity and hippocampal volume in patients with a first episode psychosis and those who meet ultra high-risk criteria. All FEP patients met PEPP-Montreal inclusion criteria: 14-35 years of age, previous treatment with antipsychotic medications for no more than 30 days, DSM-IV-R diagnosis of a psychotic disorder (non-affective or affective), a psychosis that was not substance induced, ability to communicate in either English or French, an IQ of 70 or above, and no history of organic mental disorders (e.g. epilepsy). All UHR patients met criteria for this prodromal state (as described below), were between the ages of 14-30, were not receiving antipsychotic treatment, were able to communicate
in either English or French, and did not have a history of organic brain damage or severe substance abuse. Healthy community controls were recruited via advertisements placed in local newspapers. The initial contact consisted of a telephone screening in order to rule out neurological conditions and family history of psychiatric illnesses. In addition, a modified version of the Structured Clinical Interview for the DSM-IV for non-patient populations (SCID-1/NP) was conducted to screen for past or present Axis I psychiatric disorders (First et al., 2002). The studies were approved by the institutional ethics committee and both patients and controls signed an informed consent to participate in all evaluations.

2.3. Assessments

All clinical assessments and symptom ratings were conducted by trained research staff under the supervision of a senior psychiatrist. All neuropsychological assessments were also carried out by trained research staff under the supervision of a neuropsychologist.

2.3.1. Symptoms and Diagnoses

For all FEP and UHR patients, symptom assessments were carried out every month upon entry into their respective programs until month 3 and every 3 months thereafter until the end of follow-up at 2 years. Symptom scores from the assessment conducted closest to the date of the cortisol assessment were used for analyses. Symptoms were rated on the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993) and the General Assessment of Functioning (GAF) (Endicott et al., 1976; Luborsky, 1962) was used to determine level of functioning. Diagnoses for FEP patients were
established using the Structured Clinical Interview for DSM-IV (First et al., 1997) within the first 6 months after entry into the program. A full Comprehensive Assessment for At Risk Mental States (CAARMS) (Yung et al., 2002) was conducted in order to establish UHR status and to determine which UHR criteria were met (i.e. vulnerability, attenuated symptoms, or BLIPS). The duration of untreated psychosis (DUP) was derived from the information collected during the Circumstances of Onset and Relapse Schedule (CORS) interview (Norman et al., 2004). It was calculated as the period (in weeks) between onset of psychotic symptoms and the commencement of continuous antipsychotic medication for one month or until remission of psychotic symptoms, whichever came first.

2.3.2. Medication

All antipsychotic medication dosages are described as chlorpromazine equivalents (CPZE) based on established norms (Bezchlibnyk-Butler, 2006). The following equivalencies were used for 100mg of chlorpromazine: olanzapine = 6.25 mg; haloperidol = 1.88 mg; quetiapine = 125 mg; risperidone = 0.75 mg; loxapine = 10 mg and zuclopenthixol = 120 mg (injectable every month). Medication dosage could not be calculated for FEP patients treated with long acting risperidone, paliperidone, and aripiprazole because these particular medications were not listed in the CPZE conversion table.

2.3.3. Cortisol Assessment

All participants were provided with verbal and written instructions on saliva sample collection at home using the Salivette® sampling device (Sarstedt Inc., Quebec City, Quebec, Canada) in order to assess the cortisol awakening response. They were
instructed to collect samples immediately, 30, and 60 minutes after awakening on the day of testing and to label the salivettes with the exact date and time of collection. They were further advised to refrain from consuming any food or coffee, brushing their teeth, and smoking during the sampling period. The salivettes were stored in the participants’ freezers and returned to the institute where they were stored at -20°C until they were analyzed with a time-resolved immunoassay with fluorescence detection.

2.3.4. Neuropsychological Assessment

All patients accepting treatment and follow-up at PEPP as well as CAYR were approached to complete a comprehensive neuropsychological assessment. These assessments were conducted in the patient’s language of preference (French or English). Nine commonly used tasks were used to assess performance on 6 widely studied cognitive domains (attention, verbal memory, visual memory, working memory, executive function, and processing speed). Full scale IQ was derived from the WAIS-III. Healthy community controls were administered an identical neuropsychological battery also in their language of preference. A more detailed description of the testing procedure along with descriptions of each task is provided within the manuscripts.

2.4. Data Analyses

The data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 19. Independent samples t-tests and chi-square tests were computed in order to compare demographic variables between groups. Data on neuropsychological tests where higher scores indicated worse performance (Trail-Making Test parts A and B) were inverted. Raw scores on each of the neuropsychological tests were converted to z-scores.
based on the means and standard deviations of the healthy control group. Finally, domain scores were calculated by averaging the z-scores on each individual task that assessed performance in the respective domains. Group differences on all cognitive domains were tested by conducting analysis of covariance (ANCOVA) with group (patients vs. controls) as the between subject factor and years of education as well as other relevant confounders as covariates. The CAR were tested by conducting a mixed-model ANCOVA with group as the between subject factor and time after awakening as the repeated measure. In order to obtain a single CAR value for the correlational analyses, we calculated the area under the curve with respect to the ground (AUCg) and the increase (AUCi) using a trapezoidal formula (Pruessner et al., 2003). Due to the small sample sizes for some groups and because the AUCi and AUCg were not normally distributed for all groups, Spearman’s correlations were conducted to determine the association between the CAR and cognitive function.
CHAPTER 3:

Manuscript #1:

A blunted cortisol awakening response (CAR) is differentially associated with cognitive impairments in men versus women with first-episode psychosis (FEP)

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3.1. Abstract

**Background:** Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in many clinical populations including individuals with psychotic disorders. Abnormal levels of the HPA axis hormone, cortisol, have been associated with impairments in various cognitive processes. Cognitive deficits are a key feature of psychosis and can be observed early on in the course of illness. Few studies have examined the relationship between the cortisol awakening response (CAR), a measure of HPA axis activity and cognitive function in first episode psychosis (FEP) and none have considered the effect of sex differences on this relationship. **Methods:** Eighty-two FEP patients (55 men and 27 women) and 31 healthy community controls (18 men and 13 women) were recruited to participate in the study. Saliva samples were collected to assess the CAR immediately, 30 and 60 minutes after awakening. A neuropsychological battery was administered to determine performance on six cognitive domains: attention, verbal memory, visual memory, working memory, executive function, and processing speed. From these, a global cognition score was also calculated. **Results:** The patient group as a whole had an abnormal (blunted) CAR compared to controls (F(1.85) = 3.71, p=.03) and male patients had a more blunted CAR than female patients (F(1.80) = 4.35, p=.02). In patients overall, a more blunted CAR was associated with a more severe deficit in verbal memory ($r = 0.233$, $p = 0.036$), and a lower global cognition score ($r = 0.240$, $p = 0.031$). A post-hoc examination revealed that this association was present only in female patients. In the healthy control group, there was an association between an increased CAR and worse performance in the verbal memory domain ($r = -0.393$, $p = 0.032$). **Conclusion:** The results suggest that HPA axis dysregulation, as quantified by a blunted cortisol
awakening response, plays a role in or is influenced by, cognitive function in patients with first episode psychosis, specifically in women.
3.2 Introduction:

Although the exact etiology of psychotic disorders is unknown, the stress-diathesis model provides the most parsimonious understanding of the development of psychotic disorders (Walker et al., 2008). This conceptual framework proposes that biological vulnerability and environmental stress play complementary roles in the onset and course of illness (Rosenthal, 1970; Zubin & Spring, 1977). At the biological level, the stress response is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which upon activation undergoes a cascade of events that result in the secretion of glucocorticoids (cortisol in humans). At high levels, cortisol binds to glucocorticoid receptors in the hippocampus, a structure that has been shown to play a key role the HPA axis regulatory feedback loop (Jacobson & Sapolsky, 1991). As a result, the neural stress diathesis model was proposed as an more comprehensive approach to explaining the biological mechanism linking environmental stress and the onset of psychotic disorders (Walker & Diforio, 1997).

In addition to it’s role in the HPA-axis, the hippocampus is known to play a significant role in various cognitive processes, specifically declarative memory (Eichenbaum, 1997). Chronically high levels of cortisol have been shown to result in structural and functional impairment of the hippocampus (McEwen, 1999; Sapolsky, 2003) and to be related to neurocognitive impairments (Lupien & Lepage, 2001) in many clinical and nonclinical populations including those with depression (Porter et al., 2003), PTSD (Weber et al., 2005), Cushing’s Syndrome (Starkman et al., 1992), elderly subjects (Lupien et al., 2005), and even healthy controls administered synthetic glucocorticoids (Hsu et al., 2003).
In turn, neurocognitive deficits are a core feature of psychosis with patients displaying a broad range of impairments across domains (Gold & Harvey, 1993; Kuperberg & Heckers, 2000; Sharma & Antonova, 2003). These deficits are stable over time (Gold, 2004), persist after remission of positive symptoms (Bowie & Harvey, 2006), and have been shown to effect clinical and functional outcome (Bodnar et al., 2008; Green et al., 2000). Specific impairments in memory, executive function, and processing speed have been observed early on in the course of illness with FEP patients performing at a cognitive level at least 1 standard deviation below a healthy comparison group (Mesholam-Gately et al., 2009). In addition, recent meta-analyses have confirmed that psychosis patients, even at the time of the first episode, present with reduced hippocampal volumes relative to healthy controls (Steen et al., 2006; Vita et al., 2006) and hippocampal abnormalities in schizophrenia have been shown to be associated with impairments in episodic memory (Reichenberg & Harvey, 2007).

HPA axis activity follows a diurnal pattern with a noticeable increase in circulating cortisol levels upon awakening. This phenomenon, termed the cortisol awakening response (CAR), has been established as a reliable biological measure of adrenocortical activity (Pruessner et al., 1997) and has been shown to be abnormal in many clinical populations including individuals with depression (Bhagwagar et al., 2005; Cowen, 2010; Vreeburg et al., 2009), bipolar disorder (Deshauer et al., 2003), post-traumatic stress disorder (PTSD) (Wessa et al., 2006; Yehuda, 2005), young men with Asperger syndrome (Brosnan et al., 2009) and in relation to childhood adversity (Flory et al., 2009; Heim et al., 2009; Power et al., 2012). Recently, a blunted CAR has been reported in FEP patients compared to healthy controls (Mondelli et al., 2010), while our
own group did not find a clear indication for an overall difference but noted a significantly more blunted CAR in male patients as compared to female patients (Pruessner et al., 2008; Pruessner et al., 2012).

Despite ample evidence that suggests HPA axis dysregulation may act as a mediator between the experience of stress and cognitive function this population, the area remains largely unexplored. Few studies have examined the relationship between the HPA axis and cognitive abnormalities in patients with chronic schizophrenia (Halari et al., 2004; Walder et al., 2000), and to date there has only been one study that has examined this relationship in a FEP group (Aas et al., 2011b). This study found that a blunted CAR predicts worse cognitive functioning on tasks assessing verbal memory and processing speed in a FEP group. Based on previous findings, the objectives of the present study were to, confirm the presence of a relationship between the cortisol awakening response and cognitive function, specifically in the domains of verbal memory and processing speed in a larger well-characterized FEP sample and then, to investigate the potential effect of sex on this relationship.

3.3 Method:

Treatment Setting

All patients were receiving treatment at the Prevention and Early Intervention Program for Psychoses (PEPP), Douglas Mental Health University Institute in southwest Montreal, Canada. PEPP-Montreal is the only specialized early intervention program available for this population and the hospital is the only mental health facility with no other competing
private or public hospitals in the defined catchment area. The program serves to integrate both outpatient and inpatient clinical service with research and teaching modules.

Subjects

Subjects for this study were recruited between 2005 and 2012 as part of an ongoing research project investigating stress and cortisol effects on symptom severity and hippocampal volume in first episode and at risk populations. All patients met PEPP-Montreal entry criteria (14-35 years of age, previous treatment with antipsychotic medications for less than 30 days, DSM-IV-R diagnosis of a psychotic disorder (non-affective or affective) and the ability to communicate in either English or French) and exclusion criteria (an IQ below 70, a history of organic mental disorders (e.g. epilepsy), substance induced psychosis). Age and gender matched healthy controls were recruited from the same catchment area as patients through advertisements placed in local newspapers. In an initial telephone screening, they were screened for neurological conditions, personal or family history of psychiatric illnesses, and use of medication that interferes with HPA axis function. Furthermore, a modified version of the Structured Clinical Interview for the DSM-IV for normal populations (SCID-I/NP) was conducted in order to screen for past or present psychiatric illnesses (First et al., 2002). The study was approved by the institutional ethics committee and both patients and controls signed an informed consent to participate in all evaluations.

Symptoms Assessments and Diagnoses:

In the patient group, symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993). Overall functioning and symptoms were assessed by the
Global Assessment of Functioning (GAF) scale (Endicott et al., 1976; Luborsky, 1962). Symptoms were assessed as part of the regular follow-up at PEPP and ratings based on the assessment conducted closest to the date of the CAR sample were used. Diagnoses were established by trained research staff using the Structured Clinical Interview for the DSM-IV (First et al., 1997) and were subsequently confirmed through consensus with a senior psychiatrist (A.M. and R.J.). The duration of untreated psychosis (DUP) was derived from the information collected during the Circumstances of Onset and Relapse Schedule (CORS) interview (Norman et al., 2004). It was calculated as the period (in weeks) between onset of psychotic symptoms and the commencement of continuous antipsychotic medication for one month or until remission of psychotic symptoms, whichever came first. All ratings were done by trained staff who had achieved a high level of inter-rater agreement for each rating scale (ICC varying from 0.71 to 0.88).

**Medication**

All antipsychotic medication dosages are described as chlorpromazine equivalents (CPZE) based on established norms (Bezchlibnyk-Butler, 2006). Medication dosage could not be calculated for FEP patients treated with long acting risperidone (8 men, 2 women), Paliperidone (1 man, 2 women), and Aripiprazole (1 man, 4 women) because these particular medications were not listed in the CPZE conversion table.

**Cortisol Assessment**

In order to determine the cortisol awakening response, participants were instructed to collect samples of their saliva immediately, 30, and 60 minutes after awakening on the testing day. Subjects were provided with both verbal and written instructions on how to
collect saliva samples at home using the Salivette® sampling device (Sarstedt Inc., Quebec City, Quebec, Canada). They were further instructed to refrain from eating, drinking coffee, brushing their teeth, and smoking during the entire sampling period. Participants were asked to clearly label the salivettes with the date and exact sampling time and then store them in a freezer until returning them to the institute where they were stored at -20°C until analysis. Cortisol analysis of the saliva samples was performed with a time-resolved immunoassay with fluorescence detection.

Neuropsychological Assessment

A neuropsychological assessment was conducted within the first 3 to 6 months after entry into the program in order to allow for symptom stabilization. These assessments were carried out in the patients’ language of preference (French or English) by trained research staff under the supervision of an accredited neuropsychologist (M.L). Six domains, based on recommendations of the NIMH-Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) group (Nuechterlein et al., 2004), were calculated using 9 tasks. Full scale IQ was derived from the short form of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997a). Healthy community controls were administered the same battery of tests. Standardized z-scores were calculated for each task using the means and standard deviations of the raw scores from the control group. The score on a particular domain was established by averaging the tasks that assess performance in that domain. Furthermore, based on findings that support a unitary factor model of cognition in this population (Dickinson et al., 2006), a global cognition score was calculated by averaging the z-scores of all 6 domains in order to capture
variations in deficits on several domains. The tasks that comprise each domain are described in detail below.

**Attention**

The D2 test for attention (Brickenkamp & Zillmer, 1998) is comprised of 14 lines with 47 letters each. Individuals are required to accurately cancel out as many targets as possible among distractors present in an allotted period of time. The final score is determined by subtracting the number of distracters incorrectly cancelled out from the total number of cancellations.

**Verbal Memory**

The Logical Memory subtest of the Wechsler Memory Scale – Third Edition (WMS-III) (Wechsler, 1997b) was used to assess verbal declarative memory. Specifically, the number of items correctly recalled by the participant immediately and 30 minutes after two stories were read out to them were used as indicators of immediate and delayed memory recall.

**Visual Memory**

The Visual Reproduction subtest of the Wechsler Memory Scale – Third Edition (WMS-III) (Wechsler, 1997b) was used to assess visual memory. This task is designed to assess both immediate and delayed recall of visual material. Performance on this task was determined by the number of items successfully remembered and was measured based on the accuracy of reproduced drawings.
**Working Memory**

The Digit-Span subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997a) tests verbal working memory. For this task, a series of numbers are read aloud and participants are required to repeat the numbers back to the examiner in both the same and reverse orders. The final score is comprised of the length of the longest correctly repeated sequences prior to meeting the discontinuation criterion. The discontinuation criterion is set as the failure to correctly repeat 2 consecutive sequences of equal length.

The Spatial Span subtest of the Wechsler Memory Scale III (WMS-III) (Wechsler, 1997b) tests visual working memory. The examiner begins by tapping a series of three-dimensional blocks. The participant is then required to tap the series in both the same and reverse orders. The final score is comprised of the number of blocks in the longest correctly tapped sequence prior to meeting the discontinuation criterion. The discontinuation criterion is set as the failure to correctly tap 2 consecutive sequences of equal length.

**Executive Function**

In the Block Design subtest of the WAIS-III-R (Wechsler, 1997a), the participant is instructed to reproduce patterns using up to 9 identical red and white blocks. Performance was measured by the amount of time taken to correctly reproduce the initial pattern.

The Trail Making Test, Part B (Reitan, 1992) assesses participants’ set-shifting abilities. The task requires participants to correctly alternatively connect letters and numbers. The time for completion was used as the final score.
**Processing Speed**

The Digit-Symbol Coding Task (DST) is a subtest of the WAIS-III-R (Wechsler, 1997a). For this task, participants are instructed to correctly match a set of symbols to numbers between 1 and 9 as quickly as possible during the allotted 120-second time period.

The Trail Making Test, Part A (Reitan, 1992) requires participants to connect numbers in chronological order. The time for completion was used as the final score.

**Statistical Analyses**

The data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 19. All tests were two-tailed. Scores on BPRS subscales for positive and negative symptoms as well as depression and mania are described as based on a factor analysis by Kopelowicz et al. (Kopelowicz et al., 2008). Independent t-tests were used to compare continuous variables between patients and controls and Chi-square tests for significance were employed for categorical data. We applied a log transformation to the duration of untreated psychosis variable prior to analyses because of its skewed distribution.

Cognitive performance was compared between the two groups using analysis of covariance (ANCOVA), with education, relationship status, cigarette smoking, and cannabis use as covariates. A three factor mixed design ANOVA was conducted to assess differences in CAR between patients and controls with group and sex as between subject factors and time (0, 30, and 60 minutes after awakening) as a within subject repeated factor. For correlational analyses including cortisol, we calculated the area under the curve with respect to increase (AUCi) as well as to ground (AUCg) (Pruessner et al., 2003). The AUCi and the AUCg values were not normally distributed thus non-
parametric Spearman’s correlations were used to analyze the relationship between the CAR and cognitive performance.

**Results:**

*Demographic and clinical characteristics:*

Socio-demographic and clinical characteristics of the sample are described in Table 1. The groups did not differ on age, gender, or ethnic background. However, a significantly higher proportion of individuals in the FEP group reported smoking and using cannabis and a significantly higher proportion of them were single as compared to the healthy control group. Finally, individuals in the FEP group had significantly fewer years of formal education than the healthy controls. No differences were observed between male and female FEP patients on socio-demographic variables. Male FEP patients had a significantly higher score on the BPRS mania/hostility subscale and were receiving higher doses of medication.

*Group and sex differences in cognitive function*

Figure 1. displays the neuropsychological profile of FEP patients relative to the healthy control group. FEP patients performed significantly worse on all cognitive domains (ps < .05) except for visual memory (F(1) = 0.01, p = .94) and full scale IQ (F(1) = 1.07, p = .30). The largest effect sizes were seen in the verbal memory (ES = -1.92), processing speed (ES = -1.18), and global cognition (ES = -0.80). Results of the ANCOVA show that after adjusting for education, relationship status, smoking, and drug use, the FEP group continued to show deficits in verbal memory, executive function, processing speed, and global cognition (see Table 2). No differences were observed between male and
female FEP patients on cognitive function after adjusting for medication dosage as well as BPRS manic/hostility scores.

**Group and sex differences in CAR**

One participant in the healthy control group failed to provide a CAR assessment and one FEP patient provided an incomplete CAR assessment resulting in reduced sample sizes for both groups (81 FEP and 30 Controls). We observed a time by sex effect, showing a lower CAR in men compared to women across both groups ($F(1.3) = 3.40, p=.04$). There was also a non-significant trend towards a time by group effect with FEP patients displaying a more blunted CAR compared to controls ($F(1.91) = 2.16, p=.12$). However, given that there were significant differences between these groups on potentially confounding variables (years of completed education, relationship status, smoking, and drug use), we included these variables as covariates in the analyses. The ANCOVA revealed a significant time by group interaction ($F(1.85) = 3.71, p=.03$) and resulted in a stronger time by sex interaction ($F(1.85) = 4.72, p=.01$). Analyses exploring the effect of sex in FEP patients and controls separately, revealed a blunted CAR in men compared to women in patients ($F(1.80) = 4.35, p=.02$) but not in controls ($F(1.78) = 0.82, p=.43$). Figure 2a and b show these findings.

**Cognitive function and the cortisol awakening response**

Unlike what has previously been reported, we did not observe a relationship between the CAR, as determined by the AUCi calculation, and cognitive function in our FEP sample. However, when the analyses were repeated with the AUCg calculation, a significant positive correlation was observed in patients for verbal memory ($r = 0.233, p = 0.036$) but
not for processing speed \((r = 0.114, p = 0.31)\). Additionally, we found a significant negative correlation in the control group for verbal memory \((r = -0.393, p = 0.032)\). When investigating this relationship in male and female FEP patients separately, we found no significant correlation between the AUCg of the CAR and cognitive performance in men. However, a significant positive correlation was noted in women for verbal memory \((r = 0.398, p = 0.04)\). After employing the Bonferroni correction for multiple comparisons, the correlations no longer retain a traditional level of significance. Spearman’s correlations between the CAR and cognitive tasks are presented in Table 3.

**Discussion:**

Consistent with previous research, our FEP sample showed significant cognitive deficits compared to the control subjects in all domains except for visual memory (Reichenberg *et al.*, 2009). Furthermore, patients and controls were matched on full scale IQ indicating that results related to neurocognitive performance are not likely to be influenced by IQ and therefore must be driven by the specific domains. We also confirmed previous findings of a blunted CAR in the FEP group compared to controls (Mondelli *et al.*, 2010) and a blunted CAR in male compared to female patients (Pruessner *et al.*, 2008; Pruessner *et al.*, 2012). However, the majority of our FEP group was receiving some form of treatment with antipsychotic medication (91%). This presents a systematic difference between the groups and could potentially have contributed to the blunted response seen in the patient group based on the premise that antipsychotic medication reduces cortisol levels (Cohrs *et al.*, 2006; Meltzer, 1989; Scheepers *et al.*, 2001; Wik, 1995). However, most of these findings were based on acute
administration (4-6 weeks) of the respective antipsychotic medications where as treatment was longstanding in many of our FEP patients.

Although, there was a trend for a later time of awakening in the first episode group, this did not affect the significance of the group difference as reported previously by our group (Pruessner et al., 2012). Findings concerning the effect of time of awakening on the CAR are controversial with some reports showing no association (Pruessner et al., 1997; Wust et al., 2000) and others reporting a reduced response in later awakeners (Edwards et al., 2001; Federenko et al., 2004; Kudielka & Kirschbaum, 2003).

In contrast to the findings reported by Aas and colleagues (Aas et al., 2011b), we did not observe an association between dysregulation of the HPA axis as quantified by the AUCi of the CAR and neurocognitive function in our FEP sample. However, deficits in verbal memory were associated with a blunted CAR as calculated by the AUCg in patients. Additionally, we explored the idea of an abnormal CAR being associated with overall cognitive functioning. This analysis revealed a significant positive correlation between a blunted CAR (AUCg) and a lower score global cognition score ($r = 0.240, p = 0.031$). Although the AUCi and AUCg are highly correlated calculations ($r = .426, p < .01$), effectively, they measure different aspects of HPA axis function. Where the AUCi solely considers the acute response of the HPA axis to the act of awakening as depicted by an increase in circulating cortisol levels over a specific time period, the AUCg also takes into consideration an individual’s basal levels, providing a measure that is more related to the “total hormonal output” of the system (Pruessner et al., 2003). Acute stress activates the HPA axis resulting in an elevated cortisol output. However, with the passage of time, due to the negative feedback mechanism of the HPA axis, the body could have a
counter regulatory response to chronic stress such that basal cortisol levels drop below normal as is seen in several studies examining individuals suffering from PTSD (Wessa et al., 2006; Yehuda, 2005). Factors that can lead to the experience of chronic stress such as such as childhood trauma (Morgan & Fisher, 2007) and less than optimal parental bonding (Pruessner et al., 2012) have been documented in first episode psychosis. Therefore we believe, that the AUCg calculation for the cortisol awakening response is a more useful measure and might better reflect HPA axis dysregulation at baseline due to longstanding stress exposure. In support of the neural stress-diathesis model, for this population a blunted CAR might reflect the role of chronic HPA axis dysregulation as a mediator between the experience and appraisal of stress and subsequent cognitive impairments (Walker & Diforio, 1997).

Surprisingly, contrary to the findings reported by Aas et al. (2011), we also observed a strong correlation between an increased CAR and worse performance in the verbal memory domain in our healthy control group. However, our findings are in line with a recent study that reported that a greater CAR, established by the AUCg, was related to poorer declarative memory performance in older adults (between 55 and 77 years of age) (Almela et al., 2012). The opposite directionality of correlations observed between patients and controls supports the notion of an inverted-U shape relationship between cortisol release and cognitive performance which suggests that low basal cortisol levels (due to chronic stress) or high levels in response to acute stress compromises areas of cognition involved in learning and memory (Lupien & McEwen, 1997). It can be speculated that our control subjects were experiencing acute stress which resulted in higher cortisol levels and might explain the negative relationship seen between CAR and
cognitive performance. However, subjective stress and cortisol levels at the time of
cognitive testing were not assessed as part of the present study.

While investigating the FEP group separately, we confirmed previous reports of a
more blunted CAR in men as compared to women which had been discussed as a possible
consequence of higher vulnerability to stress and for psychosis in male compared to
female patients (Pruessner et al., 2008; Pruessner et al., 2012). Interestingly, we found
that a blunted CAR was associated with verbal memory deficits exclusively in female
FEP patients with no similar association in the male patients. When we proceeded to
examine the relationship between the CAR and global cognition separately for male and
female patients, we again noted an association in females only ($r = 0.440$, $p = 0.022$).
Seeman et al (1997) reported an association between increased cortisol secretion and
decline in memory in women only (Seeman et al., 1997). Thus, perhaps women are more
sensitive to the effects of cortisol on certain cognitive domains. However studies
examining the differential effects sex on the association between the cortisol response to
an acute psychosocial stressor and cognitive performance have yielded conflicting results.
Wolf and colleagues reported an association between a higher cortisol response to a
laboratory stressor and worse performance on memory tasks in men only (Wolf et al.,
2001). In contrast, using the same paradigm, Almela and colleagues (2011) reported a
significant association between higher cortisol response to the same stressor and poorer
memory performance in only women (Almela et al., 2011). Since men in our sample
presented with a more blunted CAR than women, it is possible that beyond a certain
threshold, the CAR no longer has a measurable effect on cognitive performance.
Some methodological limitations of the present study may limit the interpretation of the results reported. Although, participants were provided with detailed instructions on home sampling procedures for the CAR, we cannot rule out instances of noncompliance. Furthermore, despite the fact that participants recorded cortisol sampling times on the collection tubes, this does not guarantee that samples were actually taken at the reported times. Furthermore, 23 patients in our FEP group (28%) had a diagnosis of an affective psychosis; 16 of which were diagnosed with bipolar disorder and 7 had a diagnosis of major depression with psychotic features. Considering that the HPA axis dysregulation profile of individuals with bipolar disorder and depression differs from that of individuals with psychosis, the inclusion of these diagnoses in our FEP group may present a systematic limitation. Future research should attempt to investigate the effect of diagnosis (affective psychosis vs. schizophrenia spectrum disorders) on the CAR. Also, a variety of factors that were not examined in the current study have been shown to effect CAR samples including sleep disturbances (Backhaus et al., 2004; Kudielka et al., 2006; Lasikiewicz et al., 2008), obesity (Duclos et al., 2012; Wallerius et al., 2003), and socioeconomic status (Clow et al., 2004; Kunz-Ebrecht et al., 2004; Wright & Steptoe, 2005). In addition, childhood trauma has been shown to affect both the CAR (Heim et al., 2008) and cognitive function (Aas et al., 2011a; Campbell et al., 2012). Also, due to the small sample size resulting from the separation of the FEP group into males and females, the findings require replication. Although, all of the healthy controls provided a CAR sample within a week of their neuropsychological assessment, there was a notable time delay between the two for most FEP patients (67%).
In conclusion, our study showed an association between HPA axis activity, quantified by a blunted cortisol awakening response, and cognitive deficits in female FEP patients. Future research should further investigate sex differences in the association between HPA axis regulation and cognition to determine if similar differences are present using other measures of HPA axis activity (e.g. diurnal cortisol measures or response to acute psychosocial stress). Although there is evidence to suggest that the CAR shows hippocampal dependency (Buchanan et al., 2004), it has been postulated that ‘reactive’ negative feedback of the HPA axis (i.e. in response to a stressor) may be more hippocampal dependent than is basal HPA axis modulation (Walker et al., 2008). In addition, the correlation between cortisol levels and memory deficits is stronger in studies using laboratory stressors than those examining the effects of chronic stress exposure (Sauro et al., 2003). Thus, it would be of interest to examine the relationship between neurocognitive function and the cortisol response to an environmental or laboratory stressor. Eventually, such research might lead to the possibility of regulating HPA axis activity in order to improve cognitive functioning in a sex specific manner.
Table 1. Group differences in sociodemographic, clinical, and potentially confounding variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEP</th>
<th>Controls</th>
<th>Statistic</th>
<th>p-value</th>
<th>FEP male</th>
<th>Controls</th>
<th>Statistic</th>
<th>p-value</th>
<th>FEP female</th>
<th>Statistic</th>
<th>p-value</th>
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<tr>
<td>Age, M(SD)</td>
<td>23.6 (4.0)</td>
<td>22.4 (3.7)</td>
<td>t = 1.5</td>
<td>.15</td>
<td>23.5 (3.6)</td>
<td>23.8 (4.8)</td>
<td>t = -.33</td>
<td>.74</td>
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<td></td>
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<tr>
<td>Gender, male n(%)</td>
<td>55 (67.5)</td>
<td>18 (58.1)</td>
<td>$\chi^2$ = .88</td>
<td>.35</td>
<td>---</td>
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<tr>
<td>Ethnicity, visible minority n(%)</td>
<td>18 (21.7)</td>
<td>8 (25.8)</td>
<td>$\chi^2$ = .22</td>
<td>.64</td>
<td>11 (20)</td>
<td>7 (25.9)</td>
<td>$\chi^2$ = .37</td>
<td>.54</td>
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<tr>
<td>Partnership, single n(%)</td>
<td>76 (91.6)</td>
<td>19 (70.4)</td>
<td>$\chi^2$ = 7.77</td>
<td>.005</td>
<td>51 (92.7)</td>
<td>24 (88.9)</td>
<td>Fisher’s exact</td>
<td>.68</td>
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<td>Years of education, M(SD)</td>
<td>12.1 (2.5)</td>
<td>13.3 (2.0)</td>
<td>t = -2.4</td>
<td>.019</td>
<td>11.8 (2.9)</td>
<td>12.5 (2.4)</td>
<td>t = -.93</td>
<td>.35</td>
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<tr>
<td>Cigarette smoking, n(%)</td>
<td>40 (51.3)</td>
<td>8 (25.8)</td>
<td>$\chi^2$ = 5.84</td>
<td>.016</td>
<td>29 (55.8)</td>
<td>11 (42.3)</td>
<td>$\chi^2$ = 1.3</td>
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<td>Drug use, n(%)</td>
<td>34 (43.6)</td>
<td>6 (19.4)</td>
<td>$\chi^2$ = 5.61</td>
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<td>24 (46.2)</td>
<td>10 (38.5)</td>
<td>$\chi^2$ = .42</td>
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<td>BPRS positive</td>
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<td>14.4 (7.7)</td>
<td>12.6 (6.1)</td>
<td>t = 1.1</td>
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<td>BPRS negative</td>
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<td>6.1 (3.1)</td>
<td>6.0 (3.2)</td>
<td>t = 0.1</td>
<td>.92</td>
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<td>9.1 (3.3)</td>
<td>7.6 (1.9)</td>
<td>t = 2.6</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS depression/anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.3 (4.2)</td>
<td>8.7 (3.1)</td>
<td>t = 0.7</td>
<td>.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS total</td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td>44.2 (14.1)</td>
<td>41.0 (12.4)</td>
<td>t = 1.0</td>
<td>.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48.1 (19.8)</td>
<td>52.1 (21.3)</td>
<td>t = 1.3</td>
<td>.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^a$DUP (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56.2 (101.5)</td>
<td>28.1 (44.5)</td>
<td>t = -0.9</td>
<td>.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication Dosage (CPZE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>199.8 (169.2)</td>
<td>131.6 (92.1)</td>
<td>t = 2.1</td>
<td>.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of Awakening (SD)</td>
<td>08:44 (01:46)</td>
<td>08:02 (01:44)</td>
<td>t = 1.9</td>
<td>.06</td>
<td>08:48 (01:50)</td>
<td>08:37 (0:1.39)</td>
<td>t = 0.4</td>
<td>.68</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ DUP values are presented in raw form; however, these were analyzed using transformed data.
Table 2. Comparison of FEP and controls on cognitive domains

<table>
<thead>
<tr>
<th>Domains</th>
<th>FEP (N = 82)</th>
<th>Controls (N=31)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D2 Test (concentration Performance)</td>
<td>153.5</td>
<td>45.3</td>
<td>180.7</td>
</tr>
<tr>
<td>Domain z-score</td>
<td>-0.69</td>
<td>1.17</td>
<td>-0.12</td>
</tr>
<tr>
<td><strong>Verbal Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>34.8</td>
<td>11.0</td>
<td>51.8</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>21.3</td>
<td>8.3</td>
<td>33.4</td>
</tr>
<tr>
<td>Domain z-score</td>
<td>-1.92</td>
<td>1.28</td>
<td>-0.18</td>
</tr>
<tr>
<td><strong>Visual Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>91.0</td>
<td>12.0</td>
<td>89.9</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>76.5</td>
<td>21.3</td>
<td>77.7</td>
</tr>
<tr>
<td>Domain z-score</td>
<td>0.02</td>
<td>1.03</td>
<td>-0.04</td>
</tr>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>16.1</td>
<td>4.2</td>
<td>17.8</td>
</tr>
<tr>
<td>Spatial span</td>
<td>16.4</td>
<td>3.7</td>
<td>17.5</td>
</tr>
<tr>
<td>Domain z-score</td>
<td>-0.40</td>
<td>0.98</td>
<td>-0.15</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test B (completion time)</td>
<td>74.6</td>
<td>30.0</td>
<td>61.5</td>
</tr>
<tr>
<td>Block Design</td>
<td>45.6</td>
<td>13.4</td>
<td>47.5</td>
</tr>
<tr>
<td>Domain z-score</td>
<td>-0.57</td>
<td>1.36</td>
<td>-0.07</td>
</tr>
<tr>
<td><strong>Processing Speed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test A (completion time)</td>
<td>33.4</td>
<td>12.4</td>
<td>25.5</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>68.4</td>
<td>15.6</td>
<td>83.1</td>
</tr>
<tr>
<td>Domain z-score</td>
<td>-1.18</td>
<td>1.28</td>
<td>-0.07</td>
</tr>
<tr>
<td><strong>General Intelligence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>98.0</td>
<td>17.5</td>
<td>101.7</td>
</tr>
<tr>
<td><strong>Global Cognition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global z-score</td>
<td>-0.80</td>
<td>0.94</td>
<td>-0.10</td>
</tr>
</tbody>
</table>
Table 3. Spearman’s correlations between CAR (AUCg) and cognitive domains (z-scores)

<table>
<thead>
<tr>
<th>Domains</th>
<th>Patients (N = 81)</th>
<th>Controls (N = 30)</th>
<th>FEP Male (N = 54)</th>
<th>FEP Female (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>0.233*</td>
<td>-0.393*</td>
<td>0.142</td>
<td>0.398*</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>0.114</td>
<td>-0.206</td>
<td>0.132</td>
<td>0.135</td>
</tr>
<tr>
<td>Global Cognition</td>
<td>0.240*</td>
<td>-0.356</td>
<td>0.173</td>
<td>0.440*</td>
</tr>
</tbody>
</table>

* p-value <0.05
Figure 1. Deficits in cognitive performance of FEP patients.

* By definition the control group had a mean score of near zero on each domain.
Figure 2. The CAR in male and female FEP patients (a) and healthy controls (b)


CHAPTER 4:

Manuscript #2:

Investigating the cortisol awakening response (CAR) and its association with cognitive function in individuals at ultra high-risk (UHR) for psychosis

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Abstract:

Background: Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in individuals with psychotic disorders. Cognitive deficits are a key feature of psychosis but it is unclear if they are present in individuals considered to be at ultra high-risk (UHR) for psychosis. Although hypercortisolemia has been shown in UHR individuals, no studies have examined the cortisol awakening response (CAR) in this population. Dysregulation of the HPA axis, expressed as an abnormal CAR, has been shown to be associated with impairments in certain cognitive processes in first episode psychosis (FEP) but has yet to be explored in an UHR group. Methods: Twenty-eight patients at UHR for psychosis (18 men and 10 women) and 31 healthy community controls (18 men and 13 women) were recruited to participate in the study. Saliva samples were collected to assess the CAR immediately, 30 and 60 minutes after awakening. A neuropsychological battery was administered to determine performance on six cognitive domains: attention, verbal memory, visual memory, working memory, executive function, and processing speed. From these, a global cognition score was also calculated. Results: Patients performed significantly worse than controls in the domains of verbal memory ($F(1) = 5.79, p = .02$) and processing speed ($F(1) = 8.68, p = .005$). No significant differences were observed between the groups on the CAR. Furthermore, there was no association between the CAR and cognitive domains in the UHR group. Conclusion: The results suggest that the cortisol awakening response is intact prior to the onset of psychosis in individuals considered to be at UHR. Although, certain cognitive domains are impaired in this group, the deficits are not associated with this measure of HPA axis dysregulation.
**Introduction:**

The development of psychosis up to the presentation of a first episode (FEP) is a gradual process that is often preceded by a period of non-specific psychiatric symptoms and/or sub threshold psychotic symptoms retrospectively known as the “prodrome.” Prospective research conducted on this period has revealed a state of ultra high risk (UHR) that is more proximal to the time of onset of psychosis (Yung et al., 1996).

Although cognitive impairment has long been recognized as a central feature of the pathophysiology of psychotic illnesses (Heinrichs, 2005; Mesholam-Gately et al., 2009; Pantelis & Maruff, 2002), it has not been operationalized into the UHR identification criteria. This is largely due to conflicting findings in the current literature. Although studies have reported deficits in UHR patients in a variety of generalized neurocognitive domains including attention, working memory, verbal memory, verbal fluency, and processing speed, negative findings have also been reported in each case (Pukrop & Klosterkötter, 2010). Moreover, others have suggested that only specific deficits in olfactory identification and spatial working memory are present prior to illness onset (Brewer et al., 2006). Findings also vary between studies that examine the UHR group as a whole and others that focus principally on those individuals that eventually convert to a full syndrome of psychosis (Brewer et al., 2006; Pukrop & Klosterkötter, 2010).

A number of neuroimaging studies have identified structural and functional brain abnormalities specifically in the prefrontal and medial temporal regions, including the hippocampus, in FEP (Adriano et al., 2012; Steen et al., 2006). These abnormalities are congruent with the neurocognitive performance deficits also observed in this group. However, studies attempting to determine the timing of these changes relative to the
emergence of a psychosis have provided inconclusive results (Pukrop & Klosterkötter, 2010; Wood et al., 2008). Since the hippocampus is also implicated in the regulatory feedback loop of the hypothalamic-pituitary-adrenal (HPA) axis (Jacobson & Sapolsky, 1991) and has been incorporated into the neural stress-diathesis model of the aetiology of schizophrenia (Walker & Diforio, 1997), significant interest has emerged in the role of the HPA axis in the UHR stage.

The stress-diathesis model proposes that environmental stress and the inability to cope with it can trigger the onset and progression of psychosis (Nuechterlein & Dawson, 1984; Rosenthal, 1970; Zubin & Spring, 1977). In testing this model, many studies have focused on the HPA axis as it is responsible for the production and regulation of cortisol and is considered a major mediator of the human stress response. In addition, it appears that the HPA axis has the potential for augmenting dopamine transmission. Since mesolimbic dopamine overactivation represents the primary abnormality in psychosis, it has been suggested that the HPA axis can be viewed as a mediator of the relationship between stress and symptom exacerbation in psychosis (Walker & Diforio, 1997). FEP patients show a specific pattern of dysregulated HPA axis activity that is expressed as elevated daytime cortisol levels (Gunduz-Bruce et al., 2007; Mondelli et al., 2010; Ryan et al., 2004) together with a blunted cortisol awakening response (CAR) (Mondelli et al., 2010; Pruessner et al., 2008; Pruessner et al., 2012). Hypercortisolemia has also been observed in UHR individuals and other prodromal groups (Thompson et al., 2007; Walker et al., 2010) but to date, none of the studies examining stress abnormalities in these populations have studied the CAR. This makes it difficult to discern whether or not a pattern of HPA axis dysregulation similar to what is seen in FEP (blunted CAR in the
context of increased diurnal levels) can also be observed prior to the onset of illness (Aiello et al., 2012). Moreover, previous research has shown an association between cognitive impairments and a blunted CAR in FEP (Aas et al., 2011). Thus the objectives of the present study are to first determine if an abnormal CAR can be observed in individuals considered to be at UHR for the development of a psychotic disorder and to investigate the relationship between the CAR and cognitive function in this group.

**Methods:**

*Treatment Setting*

Individuals at UHR were recruited from the Clinic for Assessment of Youth at Risk (CAYR), part of the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute in southwest Montreal, Canada. CAYR provides assessment, treatment (including supportive and cognitive behavioural therapy and medication for depression and anxiety when necessary) and follow-up for individuals deemed to be at ultra high risk for developing psychosis.

*Subjects*

Subjects for this study were recruited between 2005 and 2012 as part of a larger research project investigating the effects of stress and cortisol on symptom severity and hippocampal volume in first episode and at risk populations. All patients met CAYR entry criteria (14-30 years of age, not receiving antipsychotic treatment, meeting UHR criteria, the ability to communicate in either English or French). Also patients with a history of organic brain damage or severe substance abuse were excluded from the study. Healthy community controls were recruited through advertising in local newspapers. The
initial contact consisted of a telephone screening in order to rule out neurological conditions and family history of psychiatric illnesses. In addition, a modified version of the Structured Clinical Interview for the DSM-IV for non-patient populations (SCID-1/NP) was conducted to screen for past or present Axis I psychiatric disorders (First et al., 2002). The study was approved by the institutional ethics committee and both patients and controls signed an informed consent to participate in all evaluations.

**UHR Status**

Ultra high-risk status was established with the Comprehensive Assessment for At Risk Mental States (Yung et al., 2002) using widely accepted criteria which include the presence of one or more of the following 3 characteristics: 1) attenuated psychotic symptoms which includes experiencing sub threshold positive psychotic symptoms 2) brief limited intermittent psychotic symptoms (BLIPS) which are episodes of frank psychotic symptoms that have not lasted longer than a week 3) the presence of a vulnerability which consists of having a first-degree relative with a psychotic disorder coupled with a 30% decrease in functioning in the preceding year (Phillips et al., 2002).

**Symptoms**

In the UHR group, symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993). For a more meaningful analysis, BPRS subscales were calculated for positive, negative, depression/anxiety, and mania/hostility symptoms based on a previously reported factor analysis (Kopelowicz et al., 2008). Overall symptoms and functioning were assessed by the Global Assessment of Functioning (GAF) scale
(Luborsky, 1962). Ratings were based on the interview conducted closest to the date of the cortisol assessment.

**Cortisol Assessment**

The cortisol awakening response was measured via salivary samples. Participants were provided with both verbal and written instructions on how to collect saliva samples at home using the Salivette® sampling device (Sarstedt Inc., Quebec City, Quebec, Canada). They were instructed to collect samples immediately, 30, and 60 minutes after awakening on the day of testing. They were also instructed to refrain from eating, drinking coffee, brushing their teeth, and smoking throughout the entire sampling period. Participants were asked to clearly label the salivettes with the date and exact sampling time and then store them in a freezer until returning them to the institute where they were stored at -20°C until analysis. Cortisol analysis of the saliva samples was performed with a time-resolved immunoassay with fluorescence detection.

**Neuropsychological Assessment**

All individuals being followed at the CAYR clinic were approached to complete a comprehensive neuropsychological assessment. These assessments were conducted in the patients’ language of preference (French or English) by trained research staff under supervision of a certified psychologist (S.I). Six domains, based on the suggestions made by the NIMH-Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) group (Nuechterlein *et al.*, 2004), were calculated using 9 tasks that are administered as part of the neuropsychological battery. Full scale IQ was derived from the short form of the Wechsler Adult Intelligence Scale (WAIS-III)
Healthy community controls were administered the same battery of tests. Standardized z-scores were calculated for each task using the means and standard deviations of the raw scores from the control group. The score on any particular domain was established by averaging the z-scores on the individual tasks that comprise that domain. Furthermore, based on findings that support a unitary factor model of cognition (Dickinson et al., 2006), a global cognition score was calculated by averaging the z-scores of the 6 domains. Each task and the domain it assesses is described in detail below.

Attention

The D2 test for attention (Brickenkamp & Zillmer, 1998) is comprised of 14 lines with 47 letters each. Individuals are required to accurately cancel out as many targets as possible among distractors present in an allotted period of time. The final score is determined by subtracting the number of distracters incorrectly cancelled out from the total number of cancellations.

Verbal Memory

The Logical Memory subtest of the Wechsler Memory Scale – Third Edition (WMS-III) (Wechsler, 1997b) was used to assess verbal declarative memory. Specifically, the number of items correctly recalled by the participant immediately and 30 minutes after two stories were read out to them were used as indicators of immediate and delayed memory recall.
Visual Memory

The Visual Reproduction subtest of the Wechsler Memory Scale – Third Edition (WMS-III) (Wechsler, 1997b) was used to assess visual memory. This task is designed to assess both immediate and delayed recall of visual material. Performance on this task was determined by the number of items successfully remembered and was measured based on the accuracy of reproduced drawings.

Working Memory

The Digit-Span subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997a) tests verbal working memory. For this task, a series of numbers are read aloud and participants are required to repeat the numbers back to the examiner in both the same and reverse orders. The final score is comprised of the length of the longest correctly repeated sequences prior to meeting the discontinuation criterion. The discontinuation criterion is set as the failure to correctly repeat 2 consecutive sequences of equal length.

The Spatial Span subtest of the Wechsler Memory Scale III (WMS-III) (Wechsler, 1997b) tests visual working memory. The examiner begins by tapping a series of three-dimensional blocks. The participant is then required to tap the series in both the same and reverse orders. The final score is comprised of the number of blocks in the longest correctly tapped sequence prior to meeting the discontinuation criterion. The discontinuation criterion is set as the failure to correctly tap 2 consecutive sequences of equal length.
Executive Function

In the Block Design subtest of the WAIS-III-R (Wechsler, 1997a), the participant is instructed to reproduce patterns using up to 9 identical red and white blocks. Performance was measured by the amount of time taken to correctly reproduce the initial pattern.

The Trail Making Test, Part B (Reitan, 1992) assesses participants’ set-shifting abilities. The task requires participants to alternatively connect letters and numbers correctly. The time for completion was used as the final score.

Processing Speed

The Digit-Symbol Coding Task (DST) is a subtest of the WAIS-III-R (Wechsler, 1997a). For this task, participants are instructed to correctly match a set of symbols to numbers between 1 and 9 as quickly as possible during the allotted 120-second time period.

The Trail Making Test, Part A (Reitan, 1992) requires participants to connect numbers in chronological order. The time for completion was used as the final score.

Statistical Analyses

The data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 19. All tests were two tailed. Independent t-tests were used to compare continuous variables between the UHR and control groups and Chi-squares were employed for categorical data. Performance on the neuropsychological assessment was compared between the groups using analysis of covariance (ANCOVA), with age and years of education as covariates. A two factor mixed design ANCOVA was conducted to assess differences in CAR between UHR individuals and controls with group as the between
subject factor and times of the CAR sample (0, 30, 60 minutes after awakening) as the repeated factor. Spearman’s correlations were calculated to determine the association between the CAR and cognitive function. In order to obtain a single value for this analysis, we calculated the area under the curve with respect to the ground (AUCg) using a trapezoidal formula (Pruessner et al., 2003a).

**Results:**

*Demographic and Clinical Characteristics*

Twenty-eight individuals, who met criteria for ‘ultra high risk for psychosis’ (6 classified as vulnerable, 22 with attenuated symptoms, 0 with BLIPS) and 31 gender matched control subjects, completed both the neuropsychological battery. One participant in the healthy control group failed to provide a CAR assessment reducing the sample size to 30 subjects. Socio-demographic characteristics of the two groups are provided in Table 1. The groups did not differ on gender, ethnicity, relationship status, or smoking habits. There was a trend towards more drug users in the UHR group. The groups significantly differed on age and years of education with the UHR risk group being both younger ($M = 20.0, SD = 3.8$ vs. $M = 22.4, SD = 3.7$), $t(57) = -2.38, p = .02$) and having completed fewer years of formal education ($M = 11.6, SD = 2.5$ vs. $M = 13.3, SD = 2.0$), $t(57) = -2.87, p = .006$) than the healthy control group. Table 2. shows the clinical profile of the UHR group including diagnostic category, symptomology, and antidepressant treatment.

*Group differences in cognitive function*

The neuropsychological profile of UHR patients compared to the control group is shown in Fig. 1. The largest effect sizes were observed in the areas of verbal memory (ES = -
1.08) and processing speed (ES = -1.05). Results from the ANOVA show significant impairments in the UHR group compared to controls in the domains of verbal memory (F(1) = 11.54, p = .001) and processing speed (F(1) = 15.19, p < .001) as well as the global cognition measure (F(1) = 6.95, p = .01). Since the two groups presented with significant differences on the potentially confounding variables of age and years of completed formal education, these were entered as covariates. Results from the ANCOVA confirmed the deficits in verbal memory (F(1) = 5.79, p = .02) and processing speed (F(1) = 8.68, p = .005).

The cortisol awakening response and cognitive function

No significant group difference (F(1) = 0.21, p = .65) or time by group interaction (F(1.76) = 0.051, p = .93) was detected in the CAR between the UHR and control groups after adjusting for age, years of education, awakening time, and treatment with antidepressants (See Figure 2). Spearman’s correlations revealed that treatment with antidepressant medication was not correlated with the cortisol levels at the 3 times points (immediately, 30, and 60 minutes after awakening) or the AUCg. Table 3 shows Spearman’s correlations between the z-scores of the 6 cognitive domains and the AUCg of the CAR. The data show no significant relationship between the CAR and cognitive function in UHR individuals but there was a non-significant trend for an association between impaired processing speed and a smaller CAR (r = 0.348, p = 0.069).

Discussion:

In the present study we found that the UHR group presented with deficits in verbal memory and processing speed but performed at a cognitive level comparable to
that of healthy community controls in the remaining cognitive domains. This is in agreement with findings that indicate these two domains are among the first to be significantly affected early on in the course of illness (Keefe et al., 2006; Kelleher et al., 2012; Mesholam-Gately et al., 2009; Pukrop & Klosterkötter, 2010). Furthermore, verbal memory in particular has been reported as a specific deficit in FEP patients (Zanelli et al., 2010) and UHR individuals (Lenz et al., 2006).

We did not observe a difference in the cortisol awakening response between patients and healthy controls despite previous reports of basal hypercortisolemia (Thompson et al., 2007; Walker et al., 2010) in UHR individuals and higher pituitary volumes in UHR converters versus non-converters (Garner et al., 2005) as well as healthy controls (Büschlen et al., 2011). These results support the notion that the CAR is a measure distinct from but superimposed on diurnal HPA axis activity (Clow et al., 2004; Wilhelm et al., 2007). Furthermore, many of the individuals in our UHR group also had a diagnosis of depression and it has been shown that individuals with depression (Bhagwagar et al., 2005; Cowen, 2010; Vreeburg et al., 2009) and self reported depressive symptoms (Pruessner et al., 2003b) display an elevated CAR. Therefore, it is possible that these effects counter each other, resulting in the observation of a normalized CAR comparable to that of healthy controls in our UHR group.

Finally, we did not observe associations between the CAR and cognitive function in the UHR group. Individuals at high risk for developing psychosis constitute a clinically heterogeneous group many of which do not convert to a full psychotic disorder. Therefore, if the relationship between an abnormal CAR and cognitive deficits is specific to individuals with psychosis, it may emerge during or after the onset of illness making it
undetectable in this population. Furthermore, there have been findings to suggest that performance on tasks tapping into prefrontally mediated memory processes show impairment prior to the onset of a full psychotic illness, rather than performance on tasks which rely on medial-temporal-mediated memory processes (Brewer et al., 2005; Brewer et al., 2006). It has further been shown that impairments in hippocampal dependent verbal memory processes, can in fact be explained by general deficits in information processing (Leeson et al., 2010) and when performance on measures of processing speed are accounted for, no significant impairments remain in verbal memory performance (Rodriguez-Sanchez et al., 2007).

Certain methodological limitations of the present study warrant some consideration. First of all, as the cortisol samples were collected in an unsupervised environment, we cannot guarantee that they were, in fact taken at the appropriate times. Since the CAR is a time sensitive measure in that it needs to be sampled upon awakening (Wilhelm et al., 2007), time delays can result in inaccurate samples. Furthermore, although all control subjects provided their samples within a week of their neuropsychological assessment, there was a significant delay between the two assessments for many individuals in the UHR group. Also, despite the fact that treatment with antidepressants of some individuals in the UHR group was not correlated with our cortisol measure, we cannot dismiss the possibility that this may have played a role in sampling of the CAR since it has been shown that antidepressants may normalize cortisol levels (Mason & Pariante, 2006).

However, another study examining the effect of subcategories of antidepressant on HPA activity found that only tricyclic antidepressants (TCAs) had an effect on CAR levels, not
selective serotonin reuptake inhibitors (SSRIs) (Manthey et al., 2011) which was the most frequently prescribed type of antidepressant in our UHR group (21.4%).

In conclusion, the present study contributed to the current literature on cognitive deficits in individuals considered to be at UHR for psychosis and attempted to bridge a gap in the existing literature by examining HPA axis dysregulation, as quantified by the CAR, in this population. We found that verbal memory and processing speed were impaired as early as in the UHR stage but that the CAR is normal. Also, there is no association between the two during a putative state of being ultra high risk for onset of psychosis. While studying UHR groups for biological risk factors is a valuable strategy, results from such studies need to be interpreted with caution due to the heterogeneity of this population. Over the years, the conversion rates to a florid psychosis in UHR groups have been on the decline, with only about 16% of individuals identified as UHR converting to a full syndrome of psychosis within the first 2 years (Yung et al., 2008). In addition, not all individuals with psychosis report experiencing a prodromal phase. Due to the low conversion rate (7.1%) in our own sample, we were unable to examine the difference in CAR or the association between the CAR and neurocognitive performance in UHR converters versus non-converters. Thus future studies should attempt to address this area of interest. Future research might also attempt to investigate this relationship in larger UHR samples and corroborate it with neuroimaging data examining both hippocampal and pituitary volumes.
Table 1. Group differences in socio-demographic variables.

<table>
<thead>
<tr>
<th></th>
<th>UHR  ($n = 28$)</th>
<th>Controls ($n = 31$)</th>
<th>Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M(SD)</td>
<td>20.0 (3.8)</td>
<td>22.4 (3.7)</td>
<td>$t = -2.38$</td>
<td>.02</td>
</tr>
<tr>
<td>Gender, male n(%)</td>
<td>18 (64.3)</td>
<td>18 (58.1)</td>
<td>$\chi^2 = 0.40$</td>
<td>.63</td>
</tr>
<tr>
<td>Ethnicity, visible minority n (%)</td>
<td>4 (22.2)</td>
<td>8 (25.8)</td>
<td>$\chi^2 = 0.79$</td>
<td>.78</td>
</tr>
<tr>
<td>Partnership, single n(%)</td>
<td>24 (85.7)</td>
<td>19 (70.4)</td>
<td>$\chi^2 = 1.90$</td>
<td>.17</td>
</tr>
<tr>
<td>Years of education, M(SD)</td>
<td>11.6 (2.5)</td>
<td>13.3 (2.0)</td>
<td>$t = -2.87$</td>
<td>.006</td>
</tr>
<tr>
<td>Cigarette smoking, n(%)</td>
<td>3 (11.1)</td>
<td>8 (25.8)</td>
<td>$\chi^2 = 2.03$</td>
<td>.154</td>
</tr>
<tr>
<td>Drug use, n(%)</td>
<td>11 (40.7)</td>
<td>6 (19.4)</td>
<td>$\chi^2 = 3.19$</td>
<td>.074</td>
</tr>
<tr>
<td>Time of awakening (SD)</td>
<td>08:25 (01:25)</td>
<td>08:02 (01:44)</td>
<td>$t = 0.88$</td>
<td>.38</td>
</tr>
</tbody>
</table>
Table 2. Symptom and Medication Data for UHR patients

<table>
<thead>
<tr>
<th></th>
<th>UHR (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary diagnosis at baseline, N(%)</td>
<td></td>
</tr>
<tr>
<td>^{a}Vulnerability group</td>
<td>6  (21.4)</td>
</tr>
<tr>
<td>^{b}Attenuated psychosis</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>^{c}BLIPS</td>
<td>---</td>
</tr>
<tr>
<td>Antidepressant medication, N(%)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1  (3.6)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>1  (3.6)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1  (3.6)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>4  (14.3)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2  (7.1)</td>
</tr>
<tr>
<td>BPRS total, M(SD)</td>
<td>42.13 (8.22)</td>
</tr>
<tr>
<td>BPRS positive, M(SD)</td>
<td>12.00 (3.52)</td>
</tr>
<tr>
<td>BPRS negative, M(SD)</td>
<td>4.21 (1.32)</td>
</tr>
<tr>
<td>BPRS depression, M(SD)</td>
<td>11.07 (4.58)</td>
</tr>
<tr>
<td>BPRS mania, M(SD)</td>
<td>9.43 (2.28)</td>
</tr>
<tr>
<td>GAF, M(SD)</td>
<td>57.29 (12.53)</td>
</tr>
</tbody>
</table>

^{a} Family history of psychosis in first degree relative plus 30% drop in functioning in last year, sustained for a month

^{b} Subthreshold intensity or frequency of psychotic symptoms

^{c} Brief Limited Intermittent Psychotic Symptoms which spontaneous resolved within a week
Table 3. Spearman’s correlations between CAR (AUCg) and cognitive domains (z-scores)

<table>
<thead>
<tr>
<th>Domains</th>
<th>Cortisol Awakening Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UHR</td>
</tr>
<tr>
<td></td>
<td>(N = 28)</td>
</tr>
<tr>
<td>Attention</td>
<td>-0.053</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>0.068</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>0.306</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-0.167</td>
</tr>
<tr>
<td>Executive Function</td>
<td>-0.034</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>0.348</td>
</tr>
<tr>
<td>Global Cognition</td>
<td>0.120</td>
</tr>
</tbody>
</table>

* p-value < 0.05
Figure 1. Deficits in cognitive performance of FEP patients.

* By definition the control group had a mean score of near zero on each domain.
Figure 2. The CAR in UHR patients and controls before (a) and after adjusting for potential confounders (age, years of education, awakening time, antidepressant treatment (b)


executive function, and processing speed in recent-onset psychosis: 1-year 

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CHAPTER 5

General Discussion and Conclusions

5.1. Summary of Main Findings

In the first study we investigated the association between HPA axis dysregulation, as quantified by an abnormal CAR, and cognitive impairment in a large, well-characterized sample of FEP patients. The FEP group showed significant impairments in verbal memory, executive function, processing speed and global cognition compared to the matched healthy control group. In agreement with previous findings, we found that our FEP patients presented with an abnormal (blunted) CAR compared to their healthy counterparts (Mondelli et al., 2010) and that male patients presented with a more blunted CAR than female patients (Pruessner et al., 2008; Pruessner et al., 2012). In addition we observed a relationship between a blunted CAR and impairments in verbal memory and a lower global cognition score. However, further investigation attempting to discern the effect of sex on this relationship revealed that the associations observed in the complete FEP sample were in fact being driven by female patients, as we did not find any correlations between the CAR and cognition in male patients.

The second study attempted to fill a gap in the current literature on HPA axis abnormalities in the putative prodromal period proximal to the onset of psychosis by assessing the CAR in individuals considered to be at UHR for developing psychosis. Our results show that UHR individuals present with a CAR comparable to that of the healthy control group. Moreover, we also examined the neurocognitive profile of the UHR risk group. After controlling for both age and years of formal education, we found that the
UHR group performed at a cognitive level significantly below that of the control group only on measures of verbal memory and processing speed which were also compromised in the FEP group. Finally, the second study built upon the first by examining the relationship between the CAR and cognitive function in this population. Our findings indicate that although certain cognitive processes are compromised prior to the onset of a full psychotic disorder, these are not associated with the CAR during the UHR state.

5.2. Implications and Future Directions

Results from our first study offer support for the neural stress diathesis model of schizophrenia suggesting that an abnormal CAR may be reflective of chronic HPA axis dysregulation as a mediator between the experience of stress and cognitive deficits in FEP patients (Walker & Diforio, 1997). However, since we were only able to observe this relationship in female patients, it can be speculated that women may be more sensitive to the negative effects of cortisol fluctuations on cognition than men. This finding can be added to the large body of literature that shows established sex differences in schizophrenia with women exhibiting a later age of onset (Häfner, 2003; Leung, 2003; Ochoa et al., 2012; Szymanski et al., 1995), more affective (Køster et al., 2008; Leung, 2003; Ochoa et al., 2012) and paranoid (Leung, 2003) symptoms, better response to treatment (Leung, 2003; Szymanski et al., 1995) and fewer negative symptoms (Abel et al., 2010; Køster et al., 2008; Leung, 2003; Ochoa et al., 2012) than men. It would be beneficial for future studies to further explore this possibility by first examining sex differences in other measures of HPA axis activity such as diurnal cortisol levels and response to an acute psychosocial stressor and then investigating the effect they have on cognitive performance. In addition, cognitive functioning has been associated with both
clinical and functional outcomes in psychosis (Bodnar et al., 2008; Green et al., 2000) and there is evidence showing that women have better outcomes than men (Abel et al., 2010; Leung, 2003). Since our male and female FEP patients performed at a similar cognitive level and we found a relationship between CAR and cognition in females only, it can be hypothesized that stabilizing the CAR in women with FEP could lead to an improvement in cognitive functioning and result in better outcomes.

Furthermore, despite previous evidence suggesting other forms of HPA axis dysregulation in this population, we did not find an abnormal CAR in our UHR group. This is in support of the CAR representing a distinct measure of HPA axis activity (Clow et al., 2004; Wilhelm et al., 2007). Additionally, since an abnormal CAR is not present in the UHR stage, it can be speculated that this form of HPA axis dysregulation likely emerges during transition to or after the onset of a psychosis. Future studies could explore this possibility in a larger UHR group and control for the inherent heterogeneity of this population by comparing the CAR in individuals who convert to a full psychotic disorder to those who do not. This would aid in determining the time course of these changes through illness progression and guide the development of more targeted interventions so that they can be implemented during the stage where they would have maximum impact. Future research could also examine sex difference in the CAR within the UHR group to determine if these differences are present during this prodromal phase as well.

Finally, the time course and nature of the cognitive deficits observed in the progression of psychotic illnesses has been the subject of some debate due to the many conflicting findings reported from studies investigating cognitive function in UHR groups (Pukrop & Klosterkötter, 2010). In an attempt to explain these discrepant findings, it has
been proposed that prior to illness onset, impairments may only exist in very specific
cognitive processes and thus evade detection by generalized neuropsychological batteries
that are comprised of cognitively loaded tasks that employ more complex processes
(Brewer et al., 2006). The cognitive domains found to be impaired early on in the course
of illness are verbal memory and processing speed (Keefe et al., 2006; Kelleher et al.,
2012; Mesholam-Gately et al., 2009; Pukrop & Klosterkötter, 2010). Indeed, our sample
of individuals at UHR scored significantly worse than the healthy control group on tasks
measuring performance in these two domains.

5.3. Limitations

The current research presents with some methodological limitations that need to
be taken into consideration. Firstly, in both studies the CAR assessment involved saliva
sampling in an unsupervised environment where compliance to instructions could not be
monitored and was based on a single sample. Additionally, although all control subjects
provided a CAR sample within one week of the neuropsychological assessment, there
was a significant delay between the two assessments for many participants in both patient
groups. Also, our FEP group included individuals with a diagnosis of affective psychosis.
This may have had an effect our results and it differs from previous research conducted
primarily on patients with schizophrenia spectrum disorders. Future research should
attempt to investigate the effect of diagnosis on the CAR. Moreover, most of the FEP
patients were receiving antipsychotic treatment while many of the UHR individuals were
taking antidepressant medication; both of which have been shown to have an effect on
HPA axis activity (Cohrs et al., 2006; Manthey et al., 2011; Mason & Pariante, 2006;
Scheepers et al., 2001; Wik, 1995). Furthermore, separating the FEP group by sex
resulted in small sample sizes for the first study and the UHR risk group in the second study was comparable in size. Thus, findings from this research warrant replication with larger samples. In addition, we were unable to assess certain factors such as childhood trauma that are known to affect both the CAR (Heim et al., 2008) and cognition (Aas et al., 2011a; Campbell et al., 2012) thus could possibly mediate the relationship between the two. Additionally, the research was cross sectional in nature therefore the limitations associated with this method should be considered. Specifically, we were unable to assess changes in HPA axis activity with illness progression. Also, as mentioned previously, our UHR sample consisted of a heterogeneous group of help-seeking youth with a comparatively low conversation rate. Therefore, the results may not be generalizable to other settings and patient groups.

5.4. Conclusion

The inability to modulate the stress response has been a longstanding and crucial component of theories on the etiology of psychotic disorders in that the HPA axis has the potential to effect dopamine transmission. As such, many aspects of HPA axis dysregulation in the developmental course of psychotic disorders, including FEP, have become an area of great interest. Our findings support the notion that HPA axis abnormalities in FEP have a unique profile that includes a blunted cortisol awakening response that is significantly more blunted in male patients. Furthermore, although there is some evidence of elevated cortisol levels in UHR and other prodromal groups, our findings suggest that the CAR remains largely in tact prior to the onset of a psychotic disorder. Thus, HPA axis dysregulation in the prodromal phase of the illness suggests a pattern that differs from that of FEP and chronic patients. In addition, a strong consensus
exists in the literature, that generalized cognitive deficits are characteristic of schizophrenia and are apparent as early as during the presentation of a first episode (Mesholam-Gately et al., 2009; Zanelli et al., 2010) which is something we were able to show in our FEP group as well.

In conclusion, the present report has contributed to the existing literature on understanding the relationship between HPA axis dysregulation and cognitive impairments in FEP and UHR groups. Further investigating the relationship between these core features of psychotic illnesses could serve to enhance our understanding of their underlying mechanisms and guide future research. Eventually such research could lead to the possibility of developing interventions focused on regulating HPA axis activity in order to improve cognitive functioning which, in turn, could lead to improved clinical and functional outcome.


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