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Hypothalamic-pituitary-adrenal axis measures and cognitive abilities in early psychosis: Are there sex differences?

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ABSTRACT

Introduction: Measures of hypothalamic-pituitary-adrenal (HPA) axis activity such as increased diurnal cortisol levels or a blunted cortisol awakening response (CAR) have been associated with cognitive impairments in people with psychotic disorders. We aimed to explore whether there are sex differences in the relationship between HPA axis measures and cognition in early psychosis (EP).
Methods: 60 EP outpatients and 50 healthy subjects (HS) were assessed with the MATRICS Consensus Cognitive Battery. Saliva cortisol levels were determined at the neuropsychological assessment and on another day at 6 sampling times: awakening; 30′ and 60′ post-awakening; and 10:00 h, 23:00 h and 10:00 h the day after the administration of 0.25 mg of dexamethasone, which occurred at 23:00 h. Three HPA axis measures were calculated: CAR, cortisol diurnal slope and cortisol suppression ratio of the dexamethasone suppression test (DST). Multiple linear regression analyses were conducted to explore the relationship between HPA axis measures and cognitive tasks while adjusting for covariates (education level, smoking, cannabis use, and cortisol levels at the cognitive assessment). Interactions between female sex, EP diagnosis and HPA axis measures were examined.
Results: An increased CAR was associated with a poorer cognitive performance in EP women in processing speed and verbal memory. In contrast, a more flattened diurnal cortisol slope was associated with poorer functioning in the spatial working memory of EP women. DST suppression ratio was associated with better visual memory, without sex differences.
Conclusions: Our study suggests that there are sex differences in the relationship between HPA axis measures and cognitive abilities in EP.

1. Introduction

Previous studies exploring sex differences in cognitive abilities in both healthy individuals and first episode psychosis (FEP) have demonstrated a sex effect that is independent of clinical diagnosis, with better working memory in men and better verbal learning in women (Ittig et al., 2015). Although sex steroids may drive sex differences, hypothalamic-pituitary-adrenal (HPA) axis hormones may also be involved. The classical neural diathesis-stress model postulates that cortisol can increase the activity of dopamine pathways that have been implicated in schizophrenia and other psychotic disorders (Walker et al., 2008). Recent studies conducted in individuals who have a clinical high risk for psychosis (CHR) have demonstrated that HPA axis abnormalities are present before the onset of the psychotic illness; those individuals who develop a psychotic disorder have increased baseline morning salivary cortisol levels (Walker et al., 2013) or an enhanced cortisol awakening response (Labad et al., 2015). A sensitized dopaminergic response to stress has been demonstrated in CHR individuals (Mizrahi et al., 2012), supporting the neural diathesis-stress model in the risk for developing a psychotic disorder.

Chronic stress is thought to contribute to the cognitive impairment found in psychotic disorders, and other mental illnesses, via cortisol-induced 'neurotoxicity' on the hippocampus (Wolkowitz et al., 2009). In line with this hypothesis, previous studies have found a negative association between increased cortisol levels and cognitive performance in people with schizophrenia (Walder et al., 2000). In drug-free patients with schizophrenia, early morn-

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ing post-dexamethasone cortisol levels are associated with verbal learning impairment (Newcomer et al., 1991). Other classical studies in drug-free patients with schizophrenia have suggested a relationship between the baseline post-dexamethasone cortisol levels and severity of the psychotic illness in terms of negative symptoms, including affective blunting, avolition, apathy, anhedonia and attention impairment (Tandon et al., 1991). The relationship between HPA axis abnormalities and cognitive performance is not specific to individuals with schizophrenia, and this relationship has been linked to other psychiatric diagnoses, especially major depression wherein evening cortisol levels are negatively associated with verbal and working memory in psychotic depression (Gomez et al., 2006). Additionally, salivary cortisol levels over the day (area under the curve) are negatively associated with hippocampus-related neuropsychological domains (verbal and visuospatial memory) and executive function (Hinkelmann et al., 2009).

Previous studies in the field of psychosis have explored the relationship between cognitive abilities and HPA axis abnormalities at early stages of the disease. This is particularly important because both cognition and the HPA axis are altered at the onset of psychotic illness (Borges et al., 2013; Fusar-Poli et al., 2012). Studies conducted in early psychotic patients have shown associations between cortisol levels during the day and smaller hippocampal volumes (Mondelli et al., 2010). A blunted cortisol awakening response (CAR) but not cortisol levels during the day has been associated with poorer cognition in verbal memory and processing speed in individuals with first-episode psychosis (FEP) (Aas et al., 2011). Studies conducted among children who are at an elevated risk for developing schizophrenia also indicate that there is a link between HPA axis function abnormalities (higher diurnal cortisol levels and greater blunting of the CAR) and poorer performance on verbal memory and executive function (Cullen et al., 2014).

There is limited information regarding the role of sex in the relationship between hypothalamic-pituitary-adrenal (HPA) axis measures and cognitive performance in psychosis. In men with schizophrenia, higher cortisol levels during the cognitive assessment have been associated with poorer performance in processing speed (Halari et al., 2004). Other groups have reported sex differences in the relationship between CAR and hippocampal volumes has been reported in individuals with FEP, as male patients with a blunted CAR have shown reduced hippocampal volumes (Pruessner et al., 2015).

The main aim of our study was to conduct an exploratory study to address whether there are sex differences in the relationship between HPA axis measures and cognitive abilities in young individuals with early psychosis (EP).

2. Methods

2.1. Participants

We studied 60 outpatients (39 men, 21 women) with EP, aged between 18 and 35 years, from the Early Intervention Service of the Hospital Universitari Institut Pere Mata (Reus, Spain). Patients had a psychotic disorder (fulfilling DSM-IV criteria for a schizophreniform disorder [N = 14], schizophrenia [N = 10], schizoaffective disorder [N = 8] or psychotic disorder not otherwise specified [N = 28]) with a duration of illness of <3 years (65% had FEP). We used a control population of 50 healthy subjects (HS) matched by sex and age who were recruited from the community using advertisements. The exclusion criteria were severe neurological disease or mental retardation; pregnancy; language difficulties; visual impairment; alcohol, heroin or cocaine dependence; and treatment with glucocorticoids.

All procedures are in accordance with the Declaration of Helsinki. Ethical approval was obtained from the local Ethics Committee. After complete description of the study to all participants, written informed consent was obtained.

2.2. Clinical and cognitive assessment

All patients were interviewed by a psychiatrist using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). The OPCRIT checklist version 4.0 (available at http://sgdp.iop.kcl.ac.uk/opcrit/) was used to obtain DSM-IV diagnoses. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1990) was used to assess the severity of psychotic symptoms. The Calgary Depression Scale (Addington et al., 1990) was administered to assess depressive symptoms.

The Spanish version of the MATRICS Consensus Cognitive Battery (MCCB) was used to assess neurocognitive functioning (Nuechterlein et al., 2008). The MCCB contains 10 tests within 7 domains to measure cognitive functioning: speed processing, attention and vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.

Sociodemographic and clinical variables were obtained in a semi-structured interview. Consumption of alcohol was measured in standard units/day, tobacco in cigarettes/day and cannabis in joints/day. Current psychopharmacological treatment was recorded during the neuropsychological assessment. Of all 60 patients, 11 (18.3%) did not receive antipsychotic treatment, 41 (68.3%) received antipsychotic monotherapy (risperidone [n = 15], paliperidone [n = 5], olanzapine [n = 14], aripiprazole [n = 5], quetiapine [n = 1], perphenazine [n = 1]), and 8 (13.3%) received polytherapy. There were no differences in sex regarding antipsychotic treatment.

2.3. HPA axis measures

Saliva was collected from all participants with Salivette® tubes (Sarstedt AG & Co., Nümbrecht, Germany). Two saliva samples were obtained the same day of the neuropsychological assessment (before and after the MCCB administration, which was conducted in the morning, with initial assessment times ranging between 9:00 h and 12:00 h). The participants were instructed to collect 6 saliva samples at home another day at the following sampling times: awakening (T1), 30′ post-awakening (T2), 60′ post-awakening (T3), 10:00 h (T4), 23:00 h (T5) and 10:00 h the day after administration of 0.25 mg of dexamethasone, which occurred at 23:00 h (T6).

Saliva samples were processed at the Biobank from the IISPV. After centrifugation of the Salivette tubes at 3000 rpm for 5 min, the saliva was aliquoted and frozen at −20 °C until assay. Salivary cortisol was determined by a commercial chemiluminescence immunoassay (IBL, Hamburg, Germany). The intra-assay and inter-assay coefficients of variation were under 8%.

2.4. Statistical analysis

SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analyses.

We transformed cortisol values to approximate a normal distribution, as suggested by recent expert consensus guidelines (Stalder et al., 2016). A power transformation $X' = (I^{.26} - 1)/.26$ was used. Four HPA axis measures were calculated: (1) the CAR was calculated using the area under the curve with respect to increase (Pruessner et al., 2003), (2) the diurnal cortisol rhythm was calculated as the slope between the cortisol levels measured at 10:00 h and 23:00 h, (3) the cortisol suppression ratio in the dexamethasone suppression test (DST) was calculated by dividing the cortisol levels at 10:00 h by the cortisol levels at 10:00 h the morning after